# Modelling and Control of Hyperglycemia in Critical Care Patients

by

**Carmen Doran**

A thesis submitted in
fulfilment of the requirements for the
Degree of Masters of Engineering

in the

Department of Mechanical Engineering
University of Canterbury
Christchurch, New Zealand

March, 2004

# ABSTRACT

Critically ill patients are known to experience stress-induced hyperglycemia. Inhibiting the physiological response to increased glycemic levels in these patients are factors such as increased insulin resistance, increased dextrose input, absolute or relative insulin deficiency, and drug therapy. Although hyperglycemia can be a marker for severity of illness, it can also worsen outcomes, leading to an increased risk of further complications.

Hyperglycemia has been quantified in critically ill patients showing the need for glucose control. The development of a relatively simple system model and the verification of both generic and patient specific parameters have been successful in control trials and simulations over a range of critically ill patients. Stepwise reduction of blood glucose values by adaptive control was shown to be accurate to within 20 %, and average long-term fitting errors are within the measurement error of the glucose sensor.

A control algorithm capable of tight regulation for a glucose intolerant ICU patient would thus reduce mortality, as well as the burden on medical resources and time with current experience-based control approaches used in most critical care units. Overall, the research presented is a significant step towards fully automated adaptive control of hyperglycaemia in critically ill patients.

# ACKNOWLEDGEMENTS

This success of this research is attributed to a large team of people from a variety of disciplines, all helping in a vast array of areas. Foremost, I'd like to thank my supervisors, Dr. Geoff Chase from the Department of Mechanical Engineering at the University of Canterbury, and Dr. Geoff Shaw from the Department of Intensive Care Medicine at the Christchurch Hospital. The motivation and enthusiasm they have is incredibly contagious, and it was important to me to know that at any stage, they were only a phone call away. Thank you also to those that believed in me, and have supported me when the going got tough and the end seemed very far off, namely my close friends, my parents, and Aaron.

Thanks to Kate Moorhead and Nick Hudson from AIC2, for the fun year we had sorting out the whole system, especially Kate who has been a sounding board and great support over the last year as well. Also, thanks to AIC3, Pat Browne, Mike Robertson, and especially Jess Lin who is taking over the reins on the project as a PhD and who has been great to work with over the summer months. Special thanks to Max Bloomfield for his effort and perseverance in gathering data for the retrospective data audit – definitely not an easy task.

I would like to acknowledge Prof. Graeme Wake, Dr. Bob Broughton and Dr. Dominic Lee from the Mathematics and Statistics Department at Canterbury University for their help in verification of the system model developed and design and analysis of the retrospective data audit. Thanks also to Dr. Chris Hann, who has recently joined the Mechanical

Engineering Department, for his efforts in redesigning parameter identification procedures and analysis of long-term data collected.

Thank you to the critical care patients and families for their consent and their interest in the clinical trials undertaken, the nurses, clinical staff and administration staff for their time and effort during these trials, and the doctors and clinical staff for their feedback on the results encountered. Thank you to Prof. Don Beaven and Helen Lunt from the Diabetes and Lipids Research Group for their open attitude to this new research and their feedback and enthusiasm about the results obtained.

Lastly, thank you to all those that invested in this research, not for monetary gain, but because they believed it might make a difference; the ICU Trust for their financial support of AIC2, AIC3 and AIC4, Dick and Mary Earle and the rest of the board for awarding me the prestigious 'Dick and Mary Earle Scholarship in Technology', the University of Canterbury for awarding me the 'CWF Hamilton & Co Ltd Masters Scholarship in Mechanical Engineering', the New Zealand Federation of University Women for their financial support for the project and the for my trip to WC2003, and the Diabetes and Lipids Research Group.

# TABLE OF CONTENTS

# LIST OF FIGURES

# LIST OF TABLES

# 1

# INTRODUCTION AND OVERVIEW

## 1.1 MOTIVATION

Critically ill patients often experience stress-induced hyperglycemia and high levels of insulin resistance (Bloomgarden, 2003; Capes, et al., 2000; Christensen, 2001; Coursin and Murray, 2003; Esposito, et al., 2003; Finney, et al., 2003; Krinsley, 2003; McCowen, et al., 2001; Mizock, 2001; Ousman, 2002; Peck, 2004; Umpierrez, et al., 2002; Van den Berghe, et al., 2001; 2003). Nutritional support regimes with a high dextrose content often compound the counter-regulatory response, induce insulin resistance, and did not suppress endogenous glucose production as with a prandial input (McCowen, et al., 2001; Mizock, 2001; Patino, et al., 1999; Weissman, 1999). Inhibiting the physiological response to increased glycemic levels are factors such as increased insulin resistance, absolute or relative insulin deficiency, and drug therapy. Although hyperglycemia can be a marker for severity of illness, it can also worsen outcomes, leading to an increased risk of further complications, such as severe infections (Bistrian, 2001), myocardial infarctions (Capes, et al., 2000), polyneuropathy and multiple-organ failure (Van den Berghe, et al., 2001). Tight

glucose control has been shown to reduce Intensive Care Unit (ICU) patient mortality by as much as 45% (Van den Berghe, et al., 2001; 2003) if kept to a glucose level less than 6.1 mmol/L for a cardiac care population. Krinsley (2003) showed a 6 % total reduction in mortality over a broader critical care populations at a glucose limit of 7.75 mmol/L.

The aim of this research is to quantify hyperglycemia in critically ill patients, and then introduce a system model that captures the mechanisms involved and provides a means of developing control protocols. The focus on critically ill patients arises because emerging glucose sensors are still in their infancy, so it is likely that the first area for implementation of an automated approach to controlling glycemic levels is in a clinical environment. A number of recent studies have also shown reduction in mortality in critically ill patients when their glucose levels were lowered (Krinsley, 2003; Van den Berghe, et al., 2001; 2003). A control algorithm capable of tight regulation for a glucose intolerant ICU patient would thus reduce mortality, as well as the burden on medical resources and time with current experience-based control approaches used in most critical care units.

A retrospective data analysis is performed to determine how high blood glucose levels are in critical care patients and the impact of hyperglycemia on mortality, for the Christchurch Hospital ICU. Short-term and long-term analysis are presented, showing the range of applications for the control algorithm and in verifying the system model of glucose-insulin kinetics. Short-term targeted control has been clinically trialled and used to verify the system model, showing extremely good results in achieving the sub-targets set out. Long-term data fitting and predictions of retrospective data show the promise of the system

model, when teamed with a suitable controller, in both clinical situations and, eventually, for ambulatory diabetic individuals.

## 1.2 THE GLUCOSE-INSULIN SYSTEM

After food is consumed, the body reduces the complex carbohydrate and sugar molecules to the simple six-carbon sugar known as glucose. Glucose is the body's fuel, and upon the reduction by the body, it is either utilised or stored. Sensing glucose in the bloodstream leads the β-cells in the pancreas to produce insulin. The concentration of insulin acts as the body's signal as to how to manage its storage and transportation needs, and hence determines the utilisation rate of the glucose.

### *1.2.1 The Role of Insulin in the Body*

Insulin is a small protein, which consists of 51 amino acids in two closely connected chains. Insulin molecules and their connecting fragments are then packed together in small granules in the β-cells, which are secreted through the islets of Langerhans in the pancreas. Along with β-cells, the 1 to 2 million islets of Langerhans contain alpha and delta cells which secrete glucagons and somatostatin respectively, which act as additional blood glucose regulatory hormones. The alpha, beta and delta cells are approximately 25%, 60% and 10% of the total islets and are all very closely related (Guyton and Hall, 1996; Joslin, 1985).

Upon stimulation by glucose, the granules are pulled to the surface of the β-cells and the insulin molecules are released into the blood, also releasing the C-peptide connector. Therefore, C-peptide measurements are an accurate indicator of endogenous insulin production. In the blood, insulin travels in an almost entirely unbound form to the tissue receptors. A great deal of insulin is cleared from circulation within 10 - 15 minutes, with the only exception being insulin that has combined with receptors in the target cells and the small amount which is degraded by the liver, kidneys, muscle and other tissues. The rapid removal of insulin from the bloodstream is very important, quickly relaying the insulin signal to stop production of insulin as a prompt form of control.

The level of insulin in the bloodstream is the signal that facilitates the metabolic response to produce the desired effect. A high insulin level promotes storage of glucose, and a low insulin level signals the need for the release of glucose fuels, currently in storage, back into the blood stream, as shown by Figure 1.1. A meal results in an increase of insulin concentration in the blood, due to the increased secretion of insulin by the β-cells, and signals the liver and muscles to consume the extra fuel (glucose) available. The liver stores glucose as glycogen or fat, and the muscles utilise glucose primarily to repair damaged muscle cells, for energy storage as glycogen and lastly storage in the fat cells.

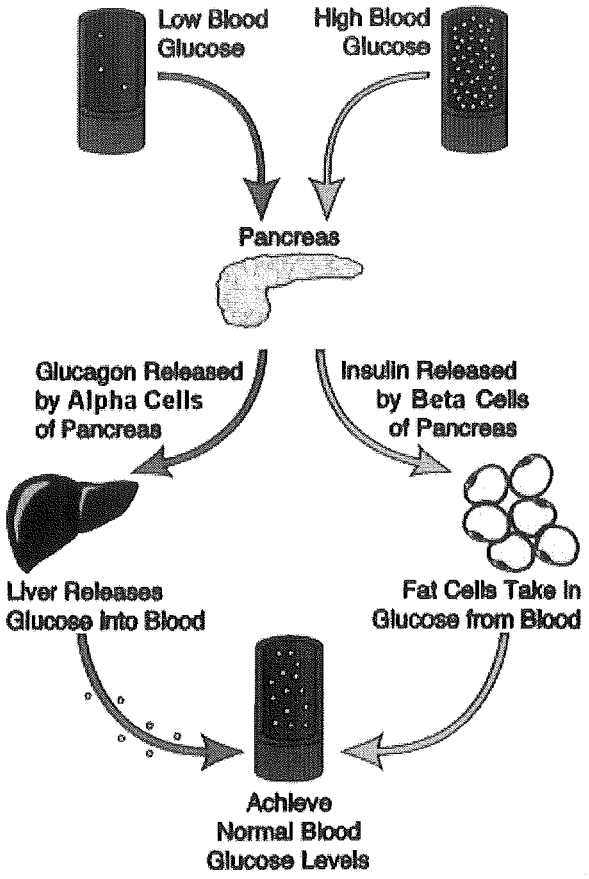


FIGURE 1.1: EFFECT OF HIGH AND LOW BLOOD GLUCOSE LEVELS ON THE BODY (ENDOCRINEWEB.COM, 2002)

When insulin levels are too high, counter regulatory hormones, such as glucagons and adrenaline, signal the liver to release glucose. If the insulin levels are significantly too high, then too much glucose is removed from the blood-stream, sometimes resulting in dangerously low blood glucose levels. When the glucose available is not sufficient to supply the brain's requirements, hyperglycemic symptoms include hunger, anxiousness, restlessness, agitation, perspiration, tachycardia (racing pulse) and palpitation (irregular and/or forced heart-beats). These symptoms are partly a result of the release of adrenalin by the body as a counter regulatory measure to restore normal blood glucose levels.

When there is a deficit in the amount of insulin released, the signal is not available to the body to indicate it should remove glucose from the blood stream. The blood-glucose level therefore rises and remains higher than the body's natural basal glucose level for an extended period, resulting in hyperglycemia. If the deficit in insulin is slight, it is probable that sufficient insulin levels will be available to control glucose in the fasting state. However, when fuel is ingested, the blood glucose level will become hyperglycemic. As the body is able to function with deficient insulin levels only in the fasting state, it is said to be lacking in glucose tolerance or glucose intolerant.

In the body's fasting state the organs must be supplied fuel (glucose) from the reserves in storage in the liver to retain function. The need for glucose reserves is indicated by a low insulin concentration in the blood. The brain is the body's priority for supply and continuously requires glucose. If the glucose is not available to supply all major organs, the energy requirement of the brain is still met by the liver's stored glycogen reserves. These priorities are shown in Figure 1.2. As the concentration of insulin signals the amount of glucose available, its role in directing glucose to the brain is vitally important. Insulin also increases the activity of other enzymes, primarily those involved in glycogen, lipid and protein synthesis, and inhibits the activity of those that catalyse glucose degradation. All major functions of insulin in the body are outlined in Figure 1.3.

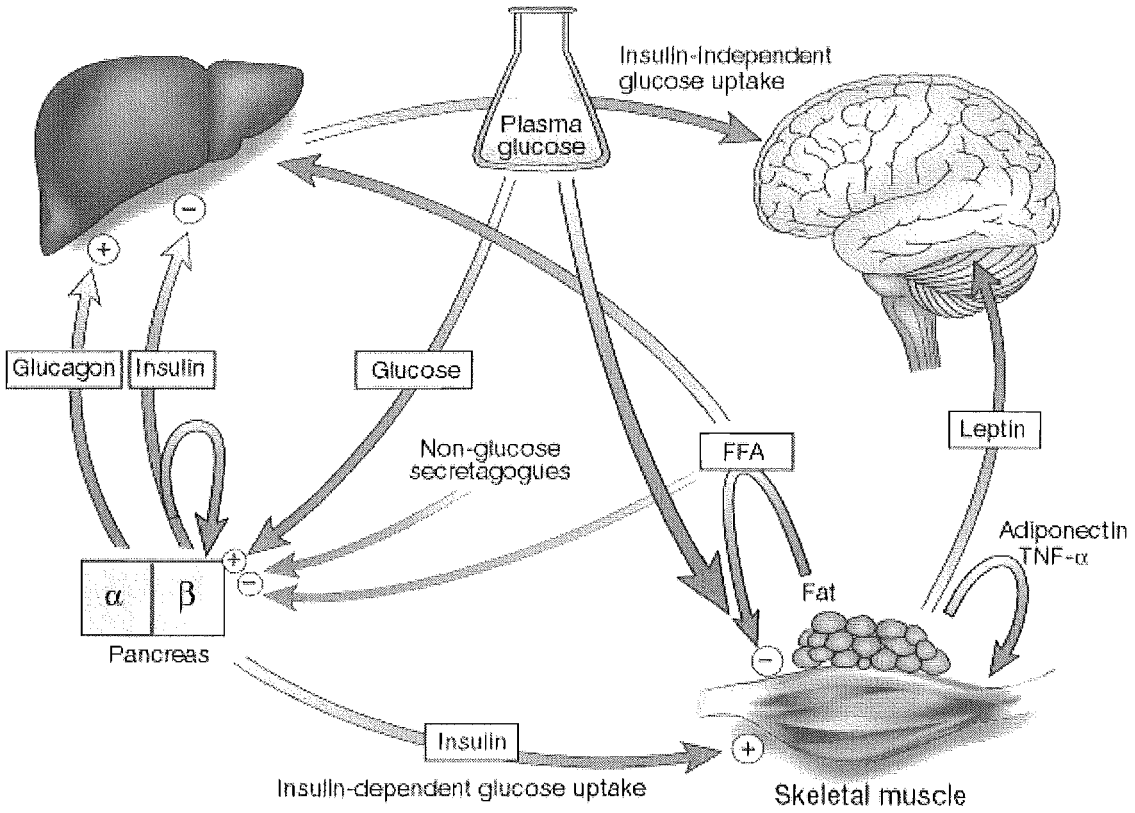


FIGURE 1.2: MAJOR ORGANS IN THE INSULIN-GLUCOSE DYNAMICS SYSTEM (SALTIEL AND KAHN, 2001)

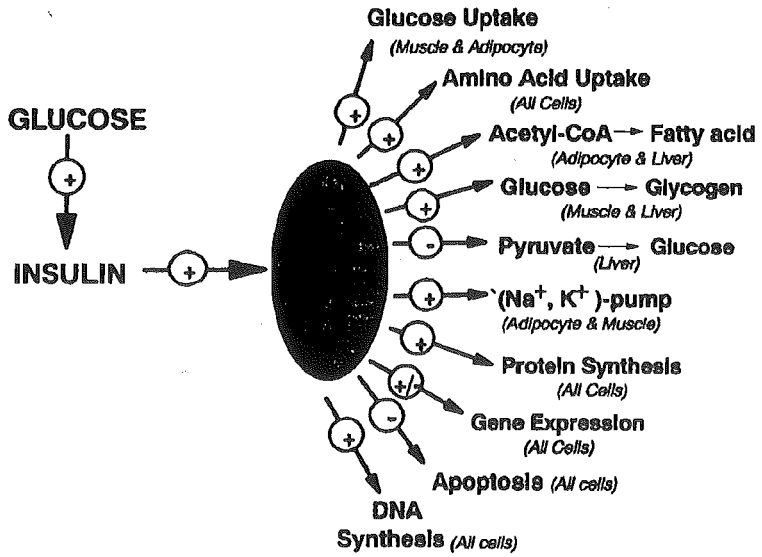


FIGURE 1.3: PHYSIOLOGICAL EFFECTS OF INSULIN.

(A '+' indicates an increase, while -' indicates a decrease in level)

### *1.2.2 Diabetes Mellitus*

Diabetes is a disorder of the metabolism where little or no insulin is produced by the β-cells, and as such blood glucose cannot be transported out of the blood. Diabetes is generally divided into two broad categories labelled Type 1 and Type 2. However, the two categories can be thought of as defining a continuum of insulin deficiency.

*Type 1 Diabetes Mellitus*

Type 1 diabetes is also known as juvenile onset diabetes, insulin dependent diabetes, or sometimes known as ketosis prone diabetes. The term juvenile onset diabetes arises as most people diagnosed with Type 1 diabetes are identified at a young age, as a result of contraction of an immune-disorder disease. Both of the other terms for Type 1 diabetic individuals come from the person's insulin dependency, as without insulin death due to ketoacidosis may occur. Type 1 diabetic individuals have little or no β-cells or β-cell function, and therefore no ability to produce insulin.

*Type 2 Diabetes Mellitus*

Type 2 diabetes is known as stable diabetes, maturity onset diabetes, or non-insulin dependent diabetes. Generally, Type 2 diabetic individuals are diagnosed in their forties or later. Although they may require small doses of insulin, it is not always completely essential for body functions. Type 2 diabetes that is not too severe can be controlled through diet and lifestyle alone.

Post-prandial glucose measurements can often be used to determine the extent of a person's β-cell function. A normal person's glucose levels should return to normal within 2 - 3 hours in response to a glucose challenge, where a Type 1 diabetic individual will not naturally return to basal and an exogenous insulin input is required. The blood glucose level of a Type 2 diabetic individual will eventually return to basal, but may require external insulin to aid in this mechanism. Each of these responses are shown schematically in Figure 1.4.

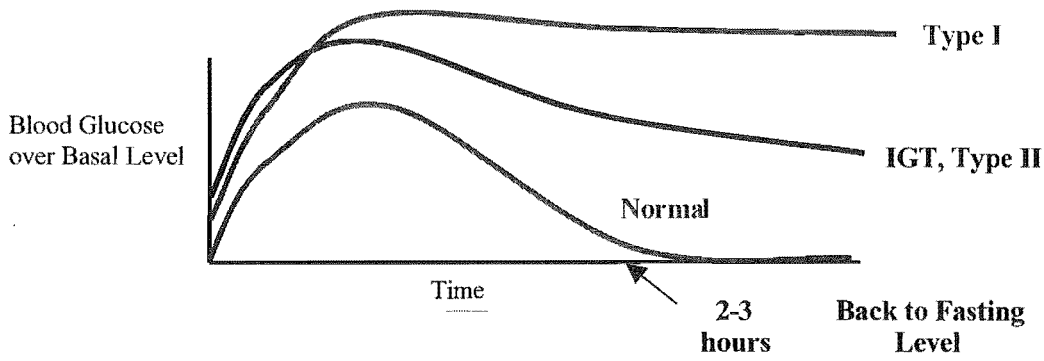


FIGURE 1.4: BLOOD GLUCOSE RESPONSE TO A GLUCOSE CHALLENGE

*Complications of Diabetes*

Lack of insulin results in blood glucose levels remaining dangerously high, which untreated over time can lead to costly complications. The risks of complications increase with the duration of the disease. Diabetic individuals are more likely to develop eye diseases such as retinopathy and cataracts, and skin disorders such as ulcers and infections, than non-diabetic individuals. Diabetic individuals also have an increased risk of heart disease, peripheral vascular (outer blood vessel) disease and cerebrovascular disease (stroke), as well as increased neuropathy (nervous system disease).

Many of the complications due to diabetes are a result of protein cross-linking that occurs in the presence of elevated blood glucose levels. Protein containing collagen fibres surround blood vessels. When these proteins form cross-links in the presence of excess glucose, the fibres loose much of their elasticity, resulting, for example, in hardening of the arteries around the heart or atherosclerosis. Atherosclerosis facilitates the formation of plaques which, when they break off, can obstruct the blood vessel resulting in heart attack.

Pathologic changes in blood vessels are a large contributor to many of these complications. The immune system also fails to function optimally in the presence of high blood glucose levels. At 8 mmol/L, the immune response is only 50 % effective, and at 10 mmol/L, the immune response is essentially completely ineffective. An ineffective immune response can have the obvious significant consequences in terms of fighting off bacterial or viral infections.

*Current Treatment of Diabetes*

Current treatment of Type 1 and severe Type 2 diabetes involves constant monitoring of the plasma glucose level and injecting insulin into the subcutaneous tissue as required and best practice was laid out by the Diabetes Control and Complications Trial Research Group (1993). Using a glucose monitoring system and an insulin pump or syringe injections, all current treatments are performed manually by the patients or, in a hospital setting, under professional care. Therefore, diabetic individuals are required to monitor food intake and daily activity to maintain blood glucose levels at an acceptable level. For ease of management, subjects are encouraged to stick to strict routines and diets to keep manual

monitoring and injections to a minimum, reducing intervention and difficulty. This regime can lead to severe limitation of the subjects' lifestyle and is prone to error. As a result, many diabetic individuals do not, or cannot, maintain tight blood glucose control, resulting in regular and continuous exposure to elevated blood glucose levels. Hence, the primary problem with current treatment is that there is no interface between the monitoring system and insulin pump to automate the treatment with stability and robustness.

### *1.2.3 Stress-induced Hyperglycemia*

Medical illness and surgery can cause a state of increased insulin resistance and consequently decreased insulin sensitivity, in both diabetic and non-diabetic patients (Bloomgarden, 2003; Capes, et al., 2000; Christensen, 2001; Coursin and Murray, 2003; Esposito, et al., 2003; Finney, et al., 2003; Krinsley, 2003; McCowen, et al., 2001; Mizock, 2001; Ousman, 2002; Umpierrez, et al., 2002; Van den Berghe, et al., 2001; 2003). Given the stress-induced insulin resistance, hyperglycemia is exacerbated by the administration of intravenous fluids containing dextrose (McCowen, et al., 2001; Mizock, 2001; Patino, et al., 1999; Weissman, 1999). Increases in glucagons, growth hormones and neurotransmitters such as adrenaline, diminish the effects of insulin, decrease the insulin secretion, and stimulate hepatic glucose production (Coursin and Murray, 2003; Finney, et al., 2003; Hanson, et al., 2000; Mizock, 2001; Ratner, 2001; Thorsteinsson, 1990; Toffolo, et al., 1980; Turnheim and Waldhausl, 1988; Van den Berghe, et al., 2001; Zierler, 1999). As a result, a critical care patient has increased blood glucose production and input, combined with decreased ability to reduce blood glucose levels.

Maintaining normal basal blood glucose levels becomes increasingly important in surgical and critically ill patients. Treatment, typically with insulin, must compensate for caloric intake, as well as the increased stress the body is subject to as it excretes adrenalin and other stress hormones. To avoid serious medical predicaments such as ketosis, white blood cell dysfunction, infection, and slowed wound healing, tight blood glucose control should be maintained. In particular, tight glucose control in surgical cardiac critical care patients has been shown to reduce mortality as much as 45 % (Van den Berghe, et al., 2001; 2003) and 6 – 10 % in general critical care populations (Krinsley, 2003).

*Current Treatment of Hyperglycemia in the ICU*

In hospital situations, the most common management of blood glucose levels is to use a 'sliding-scale' protocol to administer insulin (Albisser, et al., 1974; Chee, et al., 2002; Woolfson, 1980). An example of this method is shown in Table 1.1. However, this method is often unused by medical staff, or used only as a guide, and medical staff intuition and experience are used instead in the art of medicine. There are also many problems with the sliding scale approach, as it is strictly reactive to blood glucose levels, rather than proactive so, it can result in large swings between hypoglycemia and hyperglycemia for some patients. It has also received a measurable amount of resistance by physicians and researchers that have considered the sliding scale and found the approach to be less than satisfactory (Kletter, 1998; Queale, et al., 1997; Radack, 1997; Sawin, 1997).

TABLE 1.1: AN EXAMPLE OF A SLIDING SCALE INSULIN PROTOCOL

| Blood Glucose (mmol/L) | Sliding Scale Insulin Infusion (U/hr) |
|---|---|
| < 8 | 0 |
| 8 – 10 | 1 |
| 10 – 12 | 2 |
| 12 – 14 | 3 |
| >15 | 6 |

## 1.3 RESEARCH OBJECTIVES

The overall objective of this research is to further studies towards the ultimate goal of automating insulin infusions in critically ill patients. To reach this goal, a number of avenues are considered. The research presented focuses on:

1. quantifying the need for automated insulin infusion in the ICU
2. improving the system model
3. identifying patient specific parameters
4. verifying the system model and patient specific parameters
5. applications of the system and controllers developed

### *1.3.1 Retrospective Data Audit*

The retrospective data audit considers the blood glucose and insulin profiles of all patients with a stay greater than 72 hours in the Christchurch Hospital ICU over a period of 12

months. This data allowed a wide range of aspects to be considered, and gave quantitative values to concepts that had previously been assumed on the basis of qualitative observations. The study also provided a database of patient information for use in model verification.

### *1.3.2 System Modelling*

The system model used in this research has evolved over the previous 3 years from the original three compartment minimal model (Bergman, et al., 1985). It now comprises 2 non-linear differential equations which can be decomposed into 3 linear equations. Michaelis-Menten saturation of two different insulin kinetics is then added to these equations. The evolution from Bergman's three compartment model to the current model has been an iterative process, aiming to capture all essential dynamics while minimising complexity. This approach minimises computational effort and increases the opportunity for the model to be used in control design and by medical staff in a clinical environment where patient condition and patient specific parameters are often highly variable.

### *1.3.3 Parameter Identification*

As each research group modelling the glucose-insulin system has a different model, parameter values, their definition, and their defined effects change between models. Values from the medical literature were converted into parameters relevant to the model developed, and used as initial estimates of time-varying parameters, or as approximations to generic, constant parameters.

### *1.3.4 Model and Parameter Verification*

Parameter values were researched and physiologically valid ranges identified from the extensive literature on the subject (Araujo-Vilar, et al., 1998; Avogaro, et al., 1989; Baura, et al., 1993; Bergman, et al., 1985; 1981; 1987; Bettini, et al., 1995; Caumo, et al., 1999; Cobelli, et al., 1998; Duckworth and Kitabchi, 1981; Duncan, et al., 2003; Ellemann, et al., 1987; Furler, et al., 1985; Kobayashi, et al., 1983; Kraegen and Chisholm, 1984; McDonald, et al., 2000; Natali, et al., 2000; Nestler, et al., 1988; Pacini and Bergman, 1986; Pillonetto, et al., 2002; Prigeon, et al., 1996; Thorsteinsson, 1990; 1986; Transberg, et al., 1981; Turnheim and Waldhausl, 1988; Vicini, et al., 1997; 1999). These values were used as bounds with retrospective patient data to verify the ability of the model to capture the dynamics observed using physiologically valid values

### *1.3.5 Control Applications*

The clinical trials and retrospective data fitting presented show the efficacy of the control algorithm and system models in achieving sub-target control and effectively capturing measured glucose and values across a wide range of critically ill patients. The progression of the model throughout the clinical trials has shown merit in the results, however, ideally a larger patient cohort will be subjected to the current model in order to further analyse its effectiveness and find areas in which improvements could be made. Overall, the system model presented was able to accurately capture essential dynamics of the system exhibited by the glucose and insulin driven metabolic responses in critically ill patients over both short-term and long-term periods.

## 1.4 PRIOR CONTROL RESEARCH

### *1.4.1 The Need for Control*

While ICU patients are often sedated and in a highly monitored state, they are extremely diverse in the dynamics of their hyperglycemia. As a result, their response to a glucose input can vary significantly due to equally extreme variations in insulin levels, effective insulin utilization, glucose absorption and a variety of other factors. Therefore, fixed protocols can result in error, given the large variation in patient dynamics. Hence, this research represents a fairly extreme test of the ability of the models and control systems developed, and highlight the need for simplicity in a clinical environment.

Automated treatment promises better control of blood glucose with higher consistency and an associated reduction in related complications. Existing insulin pumps and emerging non-invasive and semi-invasive glucose monitoring systems may be easily interconnected to realise a closed loop system. Ultimately, the control unit should be able to automate 90 – 95% of the day-to-day insulin care. Therefore, the goal is to control the essential dynamics, rather than all of the dynamics and exceptional behaviours.

### *1.4.2 Practical Implementation of Control Systems*

Research undertaken by Lam et al (2002) outlined the requirements for practical implementation of a blood glucose controller for diabetic individuals based upon Bergman et al's (1985) minimal model. The aim was to develop a control method for the automation of insulin infusion that linked emerging technologies in blood glucose biosensors with insulin infusion technology. The requirements of the controller were that it had to be able to account for variations in a patient's response to a glucose input and different sensor bandwidths, while maintaining a level of simplicity and robustness. A heavy derivative controller was employed, and simulations showed that a reduction in the sampling period provided a better control response (Chase, et al., 2002; Lam, et al., 2002). The trade-off's between sampling period, sensor lag, and various control regimes were considered by simulation, an example of which is shown in Figure 1.5.

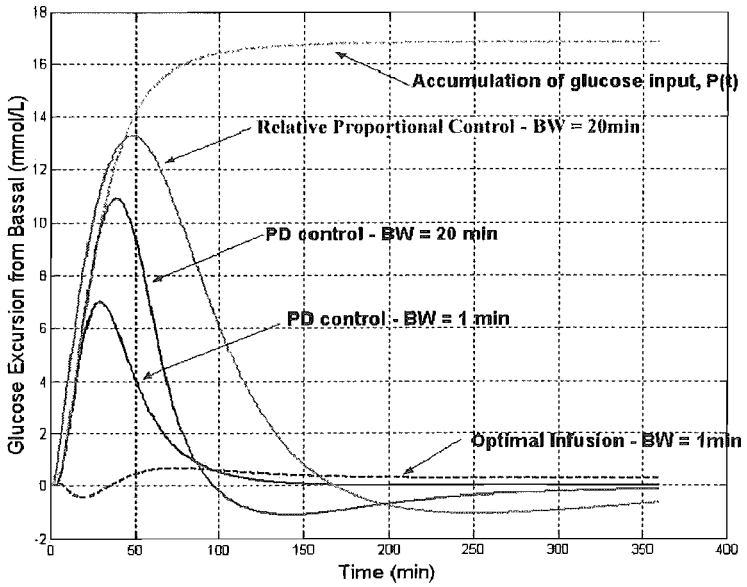


FIGURE 1.5: TYPE 1 DIABETIC INDIVIDUAL RESPONSE TO AN OGTT USING BERGMAN ET AL'S (1985) MINIMAL MODEL AND VARYING CONTROL REGIMES BY LAM ET AL (2002)

The next step was to put this theoretical work into practice. This task was undertaken by Chase et al (2003; Doran, et al., 2004a), and used the concepts developed by Lam et al (2002) to control blood glucose levels in critically ill patients. Initially, Bergman et al's (1985) original model was reduced from three-compartments to two-compartments, as critically ill patients have a direct IV line, which bypasses the subcutaneous compartment described by Bergman et al (1985). A heavy derivative controller to manage blood glucose levels following an OGTT of 75g (Chase, et al., 2003; Doran, et al., 2004a; 2004b). The test was conducted over two days, with the first day consisting of an OGTT with minimal or no insulin infusion, to determine patient specific model parameters. The second day consisted of applying the controller during an identical OGTT. The research succeeded in demonstrating tight, feedback controlled blood glucose regulation in response to a glucose input in critically ill patients using a heavy-derivative controller. The model was able to capture the insulin consumed to within 10%, and heavy derivative control was shown to result in reductions in glucose excursion of up to 89% and basal glucose reductions of up to 41% (Doran, et al., 2004a; 2004b). Figure 1.6 shows an example of the uncontrolled (day one) and controlled (day two) clinical trial.

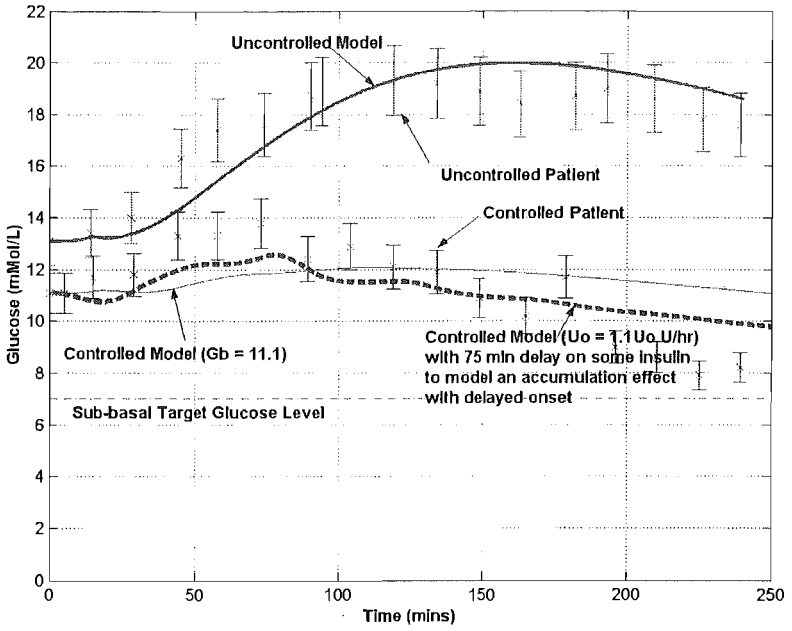


FIGURE 1.6: CONTROLLED AND UNCONTROLLED RESPONSE TO AN OGTT IN A CRITICALLY ILL PATIENT (DORAN, ET AL., 2004A; 2004B)

Albisser et al (1974) was the first researcher to explore clinical trials which showed the validity in reducing blood glucose levels using feedback control. Chee et al (2002) has also recently explored automation to manage blood glucose levels in critically ill patients. Chee et al (2002) developed a closed loop control system based on an existing 'sliding-scale' protocol, and was able to maintain blood glucose levels within the range 10 – 15 mmol/L, but not to within 6 – 10 mmol/L. Their reasoning for not obtaining lower levels was their conservativeness in insulin infusion rates to avoid hypoglycemic episodes.

Other clinical trials in the literature have focused on clamp test data (e.g. Caumo, et al., 1999; Cobelli, et al., 1998; 1999; DeFronzo, et al., 1979; Hanson, et al., 2000; Katz, et al., 2000) and have been utilised for fitting a model (e.g. Hovorka, et al., 1998a) or

identification of parameters (e.g. Araujo-Vilar, et al., 1998; Bergman, et al., 1981; Hrebicek, et al., 2002; McGuire, et al., 1979; Radziuk, 2000). A number of the clinical trials are based upon the minimal model (Bergman, et al., 1985), and some trials have found the minimal model to underestimate insulin sensitivity (e.g. Araujo-Vilar, et al., 1998; Avogaro, et al., 1989; Caumo, et al., 1999; Cobelli, et al., 1998; 1999; McDonald, et al., 2000; Radziuk, 2000; Vicini, et al., 1997; 1999) as estimating this value is often the target of these clinical studies.

Hovorka et al (2002) claim that this decreased insulin sensitivity value is due to too much modelled glucose, and modify the minimal model to a more complex model including two compartments representing the kinetics of D-[U-$^{13}$C] glucose, two compartments representing the kinetics of 3-*O*-methyl-D-glucose, and two compartments representing the kinetics of native glucose. In addition, Hovorka et al's (2002) model includes three insulin compartments representing insulin's effect on glucose distribution and transport, glucose disposal, and glucose production, resulting in 19 parameters.

Other less complex approaches based on the minimal model have used two glucose compartments (e.g. Cobelli, et al., 1999; Vicini, et al., 1999) splitting the glucose into hot and cold (traced and untraced) compartments, non-compartmental approaches (Mari, et al., 2001; Natali, et al., 2000) or have focused on insulin kinetics, primarily saturation kinetics, without considering utilisation (e.g. Home, et al., 1982; 1990; 1986; Thorsteinsson, et al., 1985). Of these trials, very few have used control algorithms or focused on developing a system model for a control application, focusing instead on fitting data retrospectively.

## 1.5 HARDWARE AVAILABLE FOR CONTROL IMPLEMENTATION

### *1.5.1 Glucose Monitoring Technology*

The fundamental aspect of ongoing treatment regimes for diabetes involves self-monitoring of blood glucose levels. The standard for obtaining a blood sample is the finger prick method. The blood sample is applied manually to a test strip and, in conjunction with a portable meter, the blood glucose measurement is found. The subject must then use their prior knowledge and experience, along with a prediction of the exercise and glucose intake they expect to experience in the next few hours, to interpret the glucose measurement and provide the insulin necessary to control their glycemic level. Monitoring of blood glucose concentration is highly important to avoid hypoglycemic and hyperglycemic incidents, however, due to the pain, hassle, and expense of testing, a number of diabetic individuals do not monitor their glucose levels as often as would be preferred by health professionals. In addition, this approach is subject to error due to misuse resulting from poor ergonomics by the diabetic individual (Rogers, et al., 2001).

Alternative sites for blood glucose sampling have been proposed in less sensitive areas of the body and devices have been developed to take these measurements. Health and industrial workers are among the groups who have found the finger as a site for blood extraction less than desirable. The AtLast meter developed by Amira Medical is early 2000 can be used in either the forearm or the thigh, whereas the Freestyle meter developed by TheraSense Inc in mid 2000 produces a "pin-head" sized blood sample painlessly from the forearm (Reynolds and Karounos, 2002). Lifescan and Abott have also introduced a number of options for alternative site testing (Johnson, et al., 2001). It should be noted that

alternative site testing may result in bruising, and that the fingertip is preferable over the forearm or thigh for detecting rapid changes in glucose levels, and hence be used for confirmation if the subject is concerned (Johnson, et al., 2001).

Beyond these choices, technological advances have lead to many options for sensing glucose levels with less invasiveness and inconvenience. The main options available on the market are the GlucoWatch Biographer from Cygnus and the Medtronic MiniMed Continuous Glucose Monitoring System (CGMS) by Paradigm (Muir, 2003). In addition, there are emerging non-invasive technologies using infra-red sensing (Anscombe, 2003).

*GlucoWatch biographer*

The GlucoWatch biographer developed by Cygnus is one of the forerunners in the field of emerging glucose sensors, providing frequent, automatic and semi-invasive glucose measurements. It works by extracting glucose through the skin using a low level current passed between a cathode and an anode in a method known as reverse iontophoresis. Uncharged glucose molecules are carried in the stream of charged sodium ions heading for the cathode, and the amount of glucose extracted is correlated to the blood glucose levels. Glucose measurement is performed using an electrochemical biosensor which detects $H_2O_2$ produced in the glucose/glucose oxidase reaction.

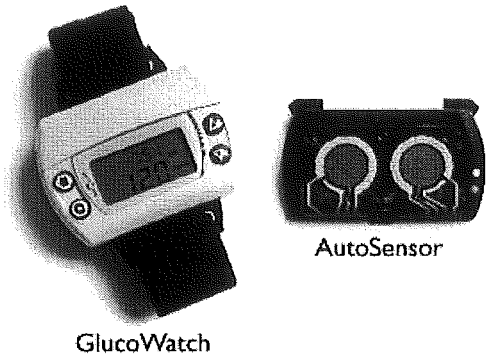


FIGURE 1.7: GLUCOWATCH AND AUTOSENSOR PADS

The GlucoWatch has limitations, with data accuracy compromised in the presence of high electrical currents or noise, open or short circuits, and excessive perspiration. Incorporated in the GlucoWatch are skin temperature and conductance sensors to detect where perspiration may have affected the reading. Predetermined criterion on the temperature and conductance sensors, and the glucose measurement output cause nonconforming readings to be skipped. A study of 13,573 biographer readings resulted in only 3.1% of skipped readings (Pitzer, et al., 2001) in semi-controlled use.

*Minimed Subcutaneous Sensor (CGMS System Gold)*

The Minimed system is more useful as a diagnostic tool than a day-to-day monitoring device, but can fulfil either role. The key components are an abdominal subcutaneous glucose sensor, and a small pager-type monitor (as shown in Figure 1.8), for diagnosis and analysis, a communication station and computer software is also required. The subcutaneous sensor can be worn for up to 72 hours, and the battery operated monitor averages the 10 second samples to display a glucose output every 5 minutes, providing 288 readings during a 24 hour period. The subject also has the option of manually entering

glucose data and event information so that when the data is downloaded, the healthcare professional has greater background knowledge to apply to analysis (Medtronic Inc, 2004; Reynolds and Karounos, 2002). Limitations include premature sensor failure resulting in loss of data, calibration issues, and the hassle involved in relocating the sensor and in keeping an event diary. However, the data density delivered is excellent and could be useful in a critical care situation given the hands-off nature of its operation.

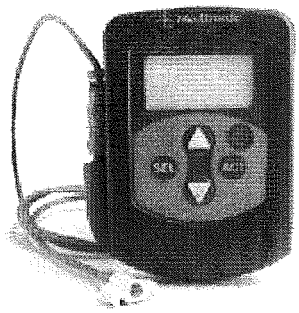

FIGURE 1.8: MEDTRONIC CGMS GLUCOSE SENSOR UNIT (MEDTRONIC INC, 2004)

### *1.5.2 Insulin Infusion Technology*

Insulin pump therapy is now used by more than 200,000 people in the United States, and it's use is growing worldwide (Nadeau, 2003). Although some diabetic individuals are unable to use insulin pumps, the majority prefer it for its convenience, flexibility, and ease of use. A study by Raskin (2003) compared efficacy, safety and patient satisfaction of Continuous Subcutaneous Insulin Infusion (CSII) using an insulin pump with Multiple Daily Injection (MDI) therapy in 132 type 2 diabetic patients. The study showed CSII

therapy and MDI therapy had comparable safety and efficacy, but 93% of the CSII treated patients preferred it to the MDI therapy.

In a clinical environment such as the ICU, drug delivery devices are commonplace and are used to give bolus or continuous infusions of multiple drugs. Currently, the insulin infusion is set by the nurse on the infusion pump, with the rate determined from the history of GlucoCard readings, knowledge of feed details, experience and intuition.

## 1.6 SUMMARY

The need for glucose control in critically ill patients cannot be debated. Though it may not be the main cause of mortality, it has been shown that it may play a large factor and is controllable with insulin, and thus should be closely monitored. The level of existing and emerging technology allows a closed-loop automated system to be realised. Given the potential liability issues of an automated insulin infusion, it is likely that the first place the system will be implemented will be in a clinical environment. Hence, the clinical application of automated insulin infusion, and the ICU in particular, is the focus for the research presented.

Feedback control has been trialled by a number of researchers, using methodology ranging from sliding-scale (Chee, et al., 2002; Van den Berghe, et al., 2001; 2003) to heavy derivative control (Chase, et al., 2002; 2003; Doran, et al., 2004a; 2004b; Lam, et al., 2002), with mixed results. Insulin infusion technology is widely accepted by both diabetic

individuals and clinical professionals and glucose sensing technology is emerging. The emerging glucose monitoring technology has been seen to have issues related to it's accuracy and efficacy (Muir, 2003; Pitzer, et al., 2001), and hence, the clinical environment is seen to be the most likely location for the introduction of automated glucose regulation. Overall, the future promises the combination of blood glucose sensors and insulin infusion technology and with the addition of a control algorithm, the development of a closed-loop feedback automated controller is imminent.

## 1.7 REFERENCES

Albisser, A. M., Leibel, B. S., Ewart, T. G., Davidovac, Z., Botz, C. K., Zingg, W., Schipper, H. and Gander, R. 1974. Clinical Control of Diabetes by the Artificial Pancreas. *Diabetes.* 23(5): 397-404

Anscombe, N. (2003). "Light Promises Painless Diabetes Management, *Biophotonics International.* Vol. December. 44-47.

Araujo-Vilar, D., Rega-Liste, C. A., Garcia-Estevez, D. A., Sarmiento-Escalona, F., Mosquera-Tallon, V. and Cabezas-Cerrato, J. 1998. Minimal Model of Glucose Metabolism: Modified Equations and Its Application in the Study of Insulin Sensitivity in Obese Subjects. *Diabetes Res Clin Pract.* 39(2): 129-141

Avogaro, A., Bristow, J. D., Bier, D. M., Cobelli, C. and Toffolo, G. 1989. Stable-Label Intravenous Glucose Tolerance Test Minimal Model. *Diabetes.* 38(8): 1048-1055

Baura, G. D., Foster, D. M., Porte, D., Jr., Kahn, S. E., Bergman, R. N., Cobelli, C. and Schwartz, M. W. 1993. Saturable Transport of Insulin from Plasma into the Central Nervous System of Dogs in Vivo. A Mechanism for Regulated Insulin Delivery to the Brain. *J Clin Invest.* 92(4): 1824-1830

Bergman, R. N., Finegood, D. T. and Ader, M. 1985. Assessment of Insulin Sensitivity in Vivo. *Endocr Rev.* 6(1): 45-86

Bergman, R. N., Phillips, L. S. and Cobelli, C. 1981. Physiologic Evaluation of Factors Controlling Glucose Tolerance in Man: Measurement of Insulin Sensitivity and Beta-Cell Glucose Sensitivity from the Response to Intravenous Glucose. *J Clin Invest.* 68(6): 1456-1467

Bergman, R. N., Prager, R., Volund, A. and Olefsky, J. M. 1987. Equivalence of the Insulin Sensitivity Index in Man Derived by the Minimal Model Method and the Euglycemic Glucose Clamp. *J Clin Invest.* 79(3): 790-800

Bettini, F., Caumo, A. and Cobelli, C. (1995). Minimal Models in Meal-Like Protocols: Simulation Studies to Assess Precision and Physiological Plausibility of Parameter Estimates. Proc *IEEE 17th Annual Conference.* 20-23 Sept. 1995. 1361-1362.

Bistrian, B. R. 2001. Hyperglycemia and Infection: Which Is the Chicken and Which Is the Egg? *JPEN J Parenter Enteral Nutr.* 25(4): 180-181

Bloomgarden, Z. T. 2003. Inflammation and Insulin Resistance. *Diabetes Care.* 26(6): 1922-1926

Capes, S. E., Hunt, D., Malmberg, K. and Gerstein, H. C. 2000. Stress Hyperglycaemia and Increased Risk of Death after Myocardial Infarction in Patients with and without Diabetes: A Systematic Overview. *Lancet.* 355(9206): 773-778

Caumo, A., Vicini, P., Zachwieja, J. J., Avogaro, A., Yarasheski, K., Bier, D. M. and Cobelli, C. 1999. Undermodeling Affects Minimal Model Indexes: Insights from a Two-Compartment Model. *Am J Physiol.* 276(6 Pt 1): E1171-1193

Chase, J. G., Lam, Z. H., Lee, J. Y. and Hwang, K. S. (2002). Active Insulin Infusion Control of the Blood Glucose Derivative. Proc *Proc. of the 7th International Conf on Control, Automation, Robotics and Vision (ICARCV 2002)* in Singapore.

Chase, J. G., Shaw, G. M., Doran, C. V., Hudson, N. H. and Moorhead, K. T. (2003). Derivative Weighted Active Insulin Control Algorithms and Trials. Proc *IFAC Symposium* in Melbourne, Australia.

Chee, F., Fernando, T. and van Heerden, P. V. 2002. Closed-Loop Control of Blood Glucose Levels in Critically Ill Patients. *Anaesth Intensive Care.* 30(3): 295-307

Christensen, D. (2001). "Critical Care: Sugar Limit Saves Lives, *Science News.* Vol. 159. 159.

Cobelli, C., Bettini, F., Caumo, A. and Quon, M. J. 1998. Overestimation of Minimal Model Glucose Effectiveness in Presence of Insulin Response Is Due to Undermodeling. *Am J Physiol.* 275(6 Pt 1): E1031-1036

Cobelli, C., Caumo, A. and Omenetto, M. 1999. Minimal Model SG Overestimation and SI Underestimation: Improved Accuracy by a Bayesian Two-Compartment Model. *Am J Physiol.* 277(3 Pt 1): E481-488

Coursin, D. B. and Murray, M. J. 2003. How Sweet Is Euglycemia in Critically Ill Patients? *Mayo Clin Proc.* 78(12): 1460-1462

DeFronzo, R. A., Tobin, J. D. and Andres, R. 1979. Glucose Clamp Technique: A Method for Quantifying Insulin Secretion and Resistance. *Am J Physiol.* 237(3): E214-223

Diabetes Control and Complications Trial Research Group. 1993. The Effect of Intensive Treatment of Diabetes on the Development and Progression of Long-Term Complications in Insulin-Dependent Diabetes Mellitus. *N Engl J Med.* 329(14): 977-986

Doran, C. V., Chase, J. G., Shaw, G. M., Moorhead, K. T. and Hudson, N. H. 2004a. Automated Insulin Infusion Trials in the ICU. *Diabetes Technology and Therapeutics.* 6(2)

Doran, C. V., Moorhead, K. T., Hudson, N. H., Chase, J. G. and Shaw, G. M. 2004b. Derivative Weighted Active Insulin Control Modelling and Clinical Trials for ICU Patients. *Med Eng Phys.* -to appear

Duckworth, W. C. and Kitabchi, A. E. 1981. Insulin Metabolism and Degradation. *Endocr Rev.* 2(2): 210-233

Duncan, G. E., Perri, M. G., Theriaque, D. W., Hutson, A. D., Eckel, R. H. and Stacpoole, P. W. 2003. Exercise Training, without Weight Loss, Increases Insulin Sensitivity and Postheparin Plasma Lipase Activity in Previously Sedentary Adults. *Diabetes Care*. 26(3): 557-562

Ellemann, K., Thorsteinsson, B., Fugleberg, S., Feldt-Rasmussen, B., Andersen, O. O., Gronbaek, P. and Binder, C. 1987. Kinetics of Insulin Disappearance from Plasma in Cortisone-Treated Normal Subjects. *Clin Endocrinol (Oxf)*. 26(5): 623-628

EndocrineWeb.com. (2002). "Normal Regulation of Blood Glucose. Vol. 2003: EndocrineWeb.com.

Esposito, K., Marfella, R. and Giugliano, D. 2003. Stress Hyperglycemia, Inflammation, and Cardiovascular Events. *Diabetes Care*. 26(5): 1650-1651

Finney, S. J., Zekveld, C., Elia, A. and Evans, T. W. 2003. Glucose Control and Mortality in Critically Ill Patients. *Jama*. 290(15): 2041-2047

Furler, S. M., Kraegen, E. W., Smallwood, R. H. and Chisholm, D. J. 1985. Blood Glucose Control by Intermittent Loop Closure in the Basal Mode: Computer Simulation Studies with a Diabetic Model. *Diabetes Care*. 8(6): 553-561

Guyton, A. C. and Hall, J. E. (1996). Insulin, Glucagon, and Diabetes Mellitus, *Textbook of Medical Physiology*. 971-983: W.B. Saunders Company.

Hanson, R. L., Pratley, R. E., Bogardus, C., Narayan, K. M., Roumain, J. M., Imperatore, G., Fagot-Campagna, A., Pettitt, D. J., Bennett, P. H. and Knowler, W. C. 2000. Evaluation of Simple Indices of Insulin Sensitivity and Insulin Secretion for Use in Epidemiologic Studies. *Am J Epidemiol*. 151(2): 190-198

Home, P. D., Massi-Benedetti, M., Gill, G. V., Capaldo, B., Shepherd, G. A. and Alberti, K. G. 1982. Impaired Subcutaneous Absorption of Insulin in 'Brittle' Diabetics. *Acta Endocrinol (Copenh)*. 101(3): 414-420

Hovorka, R., Chassin, L., Luzio, S. D., Playle, R. and Owens, D. R. 1998a. Pancreatic Beta-Cell Responsiveness During Meal Tolerance Test: Model Assessment in Normal Subjects and Subjects with Newly Diagnosed Noninsulin-Dependent Diabetes Mellitus. *J Clin Endocrinol Metab*. 83(3): 744-750

Hovorka, R., Shojaee-Moradie, F., Carroll, P. V., Chassin, L. J., Gowrie, I. J., Jackson, N. C., Tudor, R. S., Umpleby, A. M. and Jones, R. H. 2002. Partitioning Glucose Distribution/Transport, Disposal, and Endogenous Production During IVGTT. *Am J Physiol Endocrinol Metab*. 282(5): E992-1007

Hrebicek, J., Janout, V., Malincikova, J., Horakova, D. and Cizek, L. 2002. Detection of Insulin Resistance by Simple Quantitative Insulin Sensitivity Check Index QUICKI for Epidemiological Assessment and Prevention. *J Clin Endocrinol Metab*. 87(1): 144-147

Johnson, K., O'Neil, R. and Hinnen, D. 2001. Alternate Site Glucose Monitoring: A Welcome Respite. *Diabetes Spectrum.* 14: 193-194

Joslin, E. P. (1985). *Joslin's Diabetes Mellitus*: Lea & Febiger.

Katz, A., Nambi, S. S., Mather, K., Baron, A. D., Follmann, D. A., Sullivan, G. and Quon, M. J. 2000. Quantitative Insulin Sensitivity Check Index: A Simple, Accurate Method for Assessing Insulin Sensitivity in Humans. *J Clin Endocrinol Metab.* 85(7): 2402-2010

Kletter, G. G. 1998. Sliding Scale Fallacy. *Arch Intern Med.* 158(13): 1472

Kobayashi, T., Sawano, S., Itoh, T., Kosaka, K., Hirayama, H. and Kasuya, Y. 1983. The Pharmacokinetics of Insulin after Continuous Subcutaneous Infusion or Bolus Subcutaneous Injection in Diabetic Patients. *Diabetes.* 32(4): 331-336

Kraegen, E. W. and Chisholm, D. J. 1984. Insulin Responses to Varying Profiles of Subcutaneous Insulin Infusion: Kinetic Modelling Studies. *Diabetologia.* 26(3): 208-213

Krinsley, J. S. 2003. Association between Hyperglycemia and Increased Hospital Mortality in a Heterogeneous Population of Critically Ill Patients. *Mayo Clin Proc.* 78(12): 1471-1478

Lam, Z. H., Hwang, K. S., Lee, J. Y., Chase, J. G. and Wake, G. C. 2002. Active Insulin Infusion Using Optimal and Derivative-Weighted Control. *Med Eng Phys.* 24(10): 663-672

Mari, A., Pacini, G., Murphy, E., Ludvik, B. and Nolan, J. J. 2001. A Model-Based Method for Assessing Insulin Sensitivity from the Oral Glucose Tolerance Test. *Diabetes Care.* 24(3): 539-548

McCowen, K. C., Malhotra, A. and Bistrian, B. R. 2001. Stress-Induced Hyperglycemia. *Crit Care Clin.* 17(1): 107-124

McDonald, C., Dunaif, A. and Finegood, D. T. 2000. Minimal-Model Estimates of Insulin Sensitivity Are Insensitive to Errors in Glucose Effectiveness. *J Clin Endocrinol Metab.* 85(7): 2504-2508

McGuire, E. A., Tobin, J. D., Berman, M. and Andres, R. 1979. Kinetics of Native Insulin in Diabetic, Obese, and Aged Men. *Diabetes.* 28(2): 110-120

Medtronic Inc. (2004). "CGMS® System Gold™, Continuous Glucose Monitoring Overview. Vol. 2004: Medtronic Inc.

Mizock, B. A. 2001. Alterations in Fuel Metabolism in Critical Illness: Hyperglycaemia. *Best Pract Res Clin Endocrinol Metab.* 15(4): 533-551

Muir, A. (2003). New Technologies for Monitoring Metabolic Control of Diabetes in Children and Adolescents. Proc *ADA 63rd Scientific Sessions* in Louisiana. June 13 - 17, 2003.

Nadeau, D. A. (2003). Pumping Insulin: Developments in CSII. Proc *ADA 63rd Scientific Sessions* in Louisiana. June 13 - 17, 2003.

Natali, A., Gastaldelli, A., Camastra, S., Sironi, A. M., Toschi, E., Masoni, A., Ferrannini, E. and Mari, A. 2000. Dose-Response Characteristics of Insulin Action on Glucose Metabolism: A Non-Steady-State Approach. *Am J Physiol Endocrinol Metab.* 278(5): E794-801

Nestler, J. E., Clore, J. N. and Blackard, W. G. 1988. Reduced Insulin Clearance in Normal Subjects Due to Extreme Hyperinsulinemia. *Am J Med Sci.* 295(1): 15-22

Ousman, Y. 2002. Hyperglycemia in the Hospitalized Patient. *Clinical Diabetes.* 20(3): 147-148

Pacini, G. and Bergman, R. N. 1986. Minmod: A Computer Program to Calculate Insulin Sensitivity and Pancreatic Responsivity from the Frequently Sampled Intravenous Glucose Tolerance Test. *Comput Methods Programs Biomed.* 23(2): 113-122

Patino, J. F., de Pimiento, S. E., Vergara, A., Savino, P., Rodriguez, M. and Escallon, J. 1999. Hypocaloric Support in the Critically Ill. *World J Surg.* 23(6): 553-559

Peck, P. (2004). Intensive Glucose Management Reduces in-Hospital Mortality. Proc *SCCM 33rd Annual Congress* in Orlando, Florida. 20-25 February 2004.

Pillonetto, G., Sparacino, G., Magni, P., Bellazzi, R. and Cobelli, C. 2002. Minimal Model S(I)=0 Problem in NIDDM Subjects: Nonzero Bayesian Estimates with Credible Confidence Intervals. *Am J Physiol Endocrinol Metab.* 282(3): E564-573

Pitzer, K. R., Desai, S., Dunn, T., Edelman, S., Jayalakshmi, Y., Kennedy, J., Tamada, J. A. and Potts, R. O. 2001. Detection of Hypoglycemia with the Glucowatch Biographer. *Diabetes Care.* 24(5): 881-885

Prigeon, R. L., Roder, M. E., Porte, D., Jr. and Kahn, S. E. 1996. The Effect of Insulin Dose on the Measurement of Insulin Sensitivity by the Minimal Model Technique. Evidence for Saturable Insulin Transport in Humans. *J Clin Invest.* 97(2): 501-507

Queale, W. S., Seidler, A. J. and Brancati, F. L. 1997. Glycemic Control and Sliding Scale Insulin Use in Medical Inpatients with Diabetes Mellitus. *Arch Intern Med.* 157(5): 545-552

Radack, H. B. 1997. Sliding Scale Insulin Use. *Arch Intern Med.* 157(15): 1776

Radziuk, J. 2000. Insulin Sensitivity and Its Measurement: Structural Commonalities among the Methods. *J Clin Endocrinol Metab.* 85(12): 4426-4433

Raskin, P., Bode, B. W., Marks, J. B., Hirsch, I. B., Weinstein, R. L., McGill, J. B., Peterson, G. E., Mudaliar, S. R. and Reinhardt, R. R. 2003. Continuous Subcutaneous Insulin Infusion and Multiple Daily Injection Therapy Are Equally Effective in Type 2 Diabetes: A Randomized, Parallel-Group, 24-Week Study. *Diabetes Care*. 26(9): 2598-2603

Ratner, R. E. 2001. Glycemic Control in the Prevention of Diabetic Complications. *Clin Cornerstone*. 4(2): 24-37

Reynolds, L. R. and Karounos, D. G. 2002. Emerging Technology in Diabetes Mellitus: Glucose Monitoring and New Insulins. *South Med J*. 95(8): 914-918

Rogers, W., Mykityshyn, A., Campbell, R. and Fisk, A. 2001. Analysis of a 'Simple' Medical Device. *Ergonomics in Design*. Winter: 6-14

Saltiel, A. R. and Kahn, C. R. 2001. Insulin Signalling and the Regulation of Glucose and Lipid Metabolism. *Nature*. 414(6865): 799-806

Sawin, C. T. 1997. Action without Benefit. The Sliding Scale of Insulin Use. *Arch Intern Med*. 157(5): 489

Thorsteinsson, B. 1990. Kinetic Models for Insulin Disappearance from Plasma in Man. *Dan Med Bull*. 37(2): 143-153

Thorsteinsson, B., Fugleberg, S. and Binder, C. 1986. Non-Linearity of Insulin Kinetics. *Diabetologia*. 29(12): 898

Thorsteinsson, B., Fugleberg, S., Feldt-Rasmussen, B. and Binder, C. 1985. Kinetic Models for Plasma Disappearance of Insulin in Normal Subjects. *Acta Pharmacol Toxicol (Copenh)*. 57(5): 309-316

Toffolo, G., Bergman, R. N., Finegood, D. T., Bowden, C. R. and Cobelli, C. 1980. Quantitative Estimation of Beta Cell Sensitivity to Glucose in the Intact Organism: A Minimal Model of Insulin Kinetics in the Dog. *Diabetes*. 29(12): 979-990

Transberg, K., Hagander, P. and Thorell, J. 1981. Disappearance of Insulin in Man: Variation with the Plasma Insulin Level. *Acta Endocrinol (Copenh)*. 97: 391-397

Turnheim, K. and Waldhausl, W. K. 1988. Essentials of Insulin Pharmacokinetics. *Wien Klin Wochenschr*. 100(3): 65-72

Umpierrez, G. E., Isaacs, S. D., Bazargan, N., You, X., Thaler, L. M. and Kitabchi, A. E. 2002. Hyperglycemia: An Independent Marker of in-Hospital Mortality in Patients with Undiagnosed Diabetes. *J Clin Endocrinol Metab*. 87(3): 978-982

Van den Berghe, G., Wouters, P., Weekers, F., Verwaest, C., Bruyninckx, F., Schetz, M., Vlasselaers, D., Ferdinande, P., Lauwers, P. and Bouillon, R. 2001. Intensive Insulin Therapy in the Critically Ill Patients. *N Engl J Med*. 345(19): 1359-1367

Van den Berghe, G., Wouters, P. J., Bouillon, R., Weekers, F., Verwaest, C., Schetz, M., Vlasselaers, D., Ferdinande, P. and Lauwers, P. 2003. Outcome Benefit of Intensive Insulin Therapy in the Critically Ill: Insulin Dose Versus Glycemic Control. *Crit Care Med.* 31(2): 359-366

Vicini, P., Caumo, A. and Cobelli, C. 1997. The Hot IVGTT Two-Compartment Minimal Model: Indexes of Glucose Effectiveness and Insulin Sensitivity. *Am J Physiol.* 273(5 Pt 1): E1024-1032

Vicini, P., Caumo, A. and Cobelli, C. 1999. Glucose Effectiveness and Insulin Sensitivity from the Minimal Models: Consequences of Undermodeling Assessed by Monte Carlo Simulation. *IEEE Trans Biomed Eng.* 46(2): 130-137

Weissman, C. 1999. Nutrition in the Intensive Care Unit. *Crit Care.* 3(5): R67-75

Woolfson, A. M. 1980. Control of Blood Glucose During Nutritional Support in Ill Patients. *Intensive Care Med.* 7(1): 11-14

Zierler, K. 1999. Whole Body Glucose Metabolism. *Am J Physiol.* 276(3 Pt 1): E409-426

# 2

# RETROSPECTIVE DATA AUDIT

## 2.1 MOTIVATION

Critically ill patients often experience stress-induced hyperglycemia and high levels of insulin resistance, even if they have no history of diabetes (Bloomgarden, 2003; Capes, et al., 2000; Christensen, 2001; Coursin and Murray, 2003; Esposito, et al., 2003; Finney, et al., 2003; Krinsley, 2003; McCowen, et al., 2001; Mizock, 2001; Ousman, 2002; Peck, 2004; Umpierrez, et al., 2002; Van den Berghe, et al., 2001; 2003). The metabolic response to stress is characterised by major changes in glucose metabolism. Increased secretion of counter-regulatory hormones leads to a prominent rise in endogenously produced glucose and the rate of hepatic gluconeogenesis, as well as a reduction in insulin sensitivity. Nutritional support regimes with a high dextrose content often compound the counter-regulatory response and do not suppress endogenous glucose production as a meal normally would (McCowen, et al., 2001; Mizock, 2001; Patino, et al., 1999; Weissman, 1999).

Inhibiting the response to increased glycemic levels are factors such as increased insulin resistance, absolute or relative insulin deficiency, and drug therapy. Although hyperglycemia can be a marker of severity of illness, it can also worsen outcomes, leading to an increased risk of further complications, such as severe infections (Bistrian, 2001), myocardial infarctions (Capes, et al., 2000), polyneuropathy and multiple-organ failure (Van den Berghe, et al., 2001). Tight glucose control has been shown to reduce Intensive Care Unit (ICU) patient mortality by as much as 45% (Krinsley, 2003; Van den Berghe, et al., 2001; 2003).

It is debated whether the reduction in glucose levels (Van den Berghe, et al., 2001; 2003) or the administration of insulin (Annane and Melchior, 2003) is the main contributing factor for the reduction in mortality during the Van den Berghe trials. Annane and Melchior (2003) propose that the effects of insulin infusion during acute illness, such as decreased hepatic glucose production, increased immune function, and enhanced glucose transport to intracellular sites, are the reason for the reduction in the glycemic levels. However, Van den Berghe et al (2003) showed that the value of daily insulin dose was a positive, rather than a negative, risk factor for death in the patients studied indicating that it was not the amount of infused insulin that mediated the reduction of ICU mortality with intensive insulin therapy, although it is mentioned that this factor may be a contributor. Finney et al (2003) also found that it was the control of glucose levels rather than absolute levels of exogenous insulin infusions that accounted for the reduction in mortality in critically ill patients.

A retrospective data audit undertaken by Krinsley (2003) of 1826 critical care patients showed that even small increases in glycemic levels resulted in significant reduction in survival rates. Krinsley's (2003) findings showed that analysis of glucose values added predictive power above that achieved by APACHE II scores alone. McCowen et al (2001) also found a positive correlation between blood glucose values and APACHE II scores. This is a significant result as, unlike studies by Van den Berghe et al (2001; 2003) where most patients considered underwent cardiac surgery and are therefore a specific subset of critically ill patients. Both Krinsley (2003) and McCowen et al (2001) focused on large populations of heterogeneous critically ill patients. The difference between retrospective data audits, such as that by Krinsley (2003), and results of intensive insulin therapy, such as those by Van den Berghe et al (2001; 2003), is that retrospective data audits do not provide information as to whether hyperglycemia is causal of mortality, or merely a co-incidence.

The mechanisms that correlate the increased values of glucose and the increased risk of mortality are not fully understood, and many reviewers are calling for more trials on this subject (Bistrian, 2001; Esposito, et al., 2003; McCowen, et al., 2001; Mizock, 2001; Robinson, 2002). Although hyperglycemia may not be the most important factor, in reducing ICU mortality, it is definitely a contributing factor. It is also comparatively treatable and avoidable through better design of nutritional and insulin infusion regimes. Therefore, there is definitely ground for improved insulin therapy leading to euglycemic control in critically ill patients.

## 2.2 STATISTICAL METHODS AND PATIENT DESCRIPTION

### *2.2.1 Statistical Analysis*

Statistical analysis was performed using the StatXact package. Glucose values, insulin values, age, length of stay and APACHE II scores were compared between survivors and non-survivors using the exact Wilcoxon-Mann-Whitney 2-sided test. Fishers Exact 2-sided test was used for comparing study proportions between the Christchurch Hospital ICU and the Stamford Hospital ICU (Krinsley, 2003), checking the effect of gender on mortality, and comparing mechanical ventilation rates between survivors and non-survivors. Statistical significance was defined as $P < 0.05$ throughout.

### *2.2.2 Study Outline and Methods*

Between 1st January 2003 and 31st December 2003, 1164 patients were admitted to the Christchurch Hospital ICU. Of these, 237 adult patients had a stay greater than 3.0 days and were considered for analysis as Van den Berghe et al's (2001) study did not show significant changes in mortality below this value. Of these patients, 36 had no recorded plasma glucose levels and were excluded. Plasma glucose values and insulin infusions from the bedside charts for the 201 patients were recorded, along with age, sex, APACHE II score, length of stay, ICU mortality, mechanical ventilation status and primary diagnosis. The patients were divided into the categories used by Krinsley (2003) depending on their primary diagnosis, as shown in Table 2.1.

TABLE 2.1: CHRISTCHURCH HOSPITAL ICU PATIENT SUBGROUPS

| Subgroup | No of Patients | % of total |
|---|---|---|
| Cardiac | 32 | 16% |
| Pulmonary | 34 | 17% |
| Sepsis | 15 | 7% |
| Other Medical | 26 | 13% |
| Neurologic | 19 | 9% |
| General Surgical | 41 | 20% |
| Trauma | 34 | 17% |
| **TOTAL** | **201** | **100%** |

Krinsley (2003) had a similar subset of patients, as shown in Table 2.2. The major difference between this data audit and the one undertaken by Krinsley (2003) is the size of the populations examined, as the spread across patient subsets is relatively similar. The Christchurch ICU had a smaller proportion of cardiac patients (16% compared to 30%, $P < 0.0001$), as they considered both ICU and Cardiac ICU (CICU) patients, and a higher proportion of trauma patients (17% compared to 4%, $P < 0.0001$).

Finally, the study generally referred to regarding the benefits of controlling blood glucose levels is that of Van den Berghe et al (2001; 2003). The data in Table 2.1 and Table 2.2 are a more heterogeneous subset of patients than those examined by Van den Berghe et al (2001) whose study population consisted of 63% cardiac surgery patients.

TABLE 2.2: STAMFORD HOSPITAL ICU PATIENT SUBGROUPS (KRINSLEY, 2003)

| Subgroup | No of Patients | % of total |
|---|---|---|
| Cardiac | 540 | 30% |
| Pulmonary | 289 | 16% |
| Sepsis | 92 | 5% |
| Other Medical | 272 | 15% |
| Neurologic | 241 | 13% |
| General Surgical | 313 | 17% |
| Trauma | 79 | 4% |
| **TOTAL** | **1826** | **100%** |

### *2.2.3 General Patient Description*

Table 2.3 gives an overview of the patient categories. The APACHE II score was calculated from the time at which their condition was at its worst during the first 24 hours of their stay in ICU. APACHE II scores were available for 144 patients (72% of patients), and the average and range of values are for the APACHE II scores available. Length of Stay (LOS) is shown here in increments of 0.1, and the minimum length of stay is 3.0 days as patient records for those with less than 72 hours stay were excluded. The variables age, APACHE II score and length of stay are expressed as the mean, followed by the range in brackets. The survival status relates to the ICU discharge and was obtained from ICU discharge records.

As shown in Table 2.3, survival rates were highest in cardiac, sepsis and trauma patients, and lowest in pulmonary patients. Cardiac patients tended to be older and have a shorter period of stay in the ICU. Pulmonary patients were less likely to require mechanical ventilation, while trauma patients tended to be younger, predominantly male, and require mechanical ventilation. Overall, patients were younger in the Christchurch Hospital study with an average of 55.6 years compared to 62.2 and 64.3 years (Van den Berghe, et al., 2001) and 65.3 years (Krinsley, 2003). Across all three studies, patients were more likely to be male (61% compared to 71% (Van den Berghe, et al., 2001) and 54% (Krinsley, 2003)).

TABLE 2.3: GENERAL DESCRIPTION OF PATIENTS IN CHRISTCHURCH HOSPITAL ICU

| Subgroup | No of Patients | Age (years) | Female | APACHE II | Mech. Vent | LOS (days) | ICU Survival |
|---|---|---|---|---|---|---|---|
| Cardiac | 32 | 65.3 (30 - 85) | 31% | 22.1 (8 – 39) | 78% | 6.4 (3.0 – 21.8) | 94% |
| Pulmonary | 34 | 59.0 (18 – 82) | 56% | 25.5 (15 – 36) | 38% | 11.5 (3.1 – 36.0) | 71% |
| Sepsis | 15 | 55.4 (1 – 82) | 47% | 26.3 (21 – 30) | 60% | 12.0 (3.0 – 39.9) | 93% |
| Other Medical | 26 | 54.2 (20 – 84) | 58% | 25.6 (17 – 36) | 54% | 10.5 (3.0 – 35.0 | 85% |
| Neurologic | 19 | 54.1 (1 – 81) | 42% | 18.1 (7 – 24) | 74% | 8.5 (3.2 – 43.8) | 84% |
| General Surgical | 41 | 64.6 (17 – 85 | 32% | 21.5 (10 – 41) | 68% | 10.6 (3.0 – 42.5) | 88% |
| Trauma | 34 | 34.5 (15 – 83) | 18% | 17.2 (8 – 30) | 85% | 10.7 (3.0 – 60.0 | 94% |
| **TOTAL** | **201** | **55.6 (1 – 85)** | **39%** | **21.8 ( 7 – 41)** | **66%** | **9.9 (3.0 – 60.0)** | **87%** |

Age, APACHE II score and LOS are expressed as 'mean (range)'

### *2.2.4 Length of Stay*

Figure 2.1 shows the distribution of length of stay for the patients studied. Patients with a stay of 3 – 4 days made up 19.1% of the patient population studied, while patients with 3 - 9 days stay made up 62.4% of the population. The longest length of stay in the ICU during 2003 was 60.0 days.

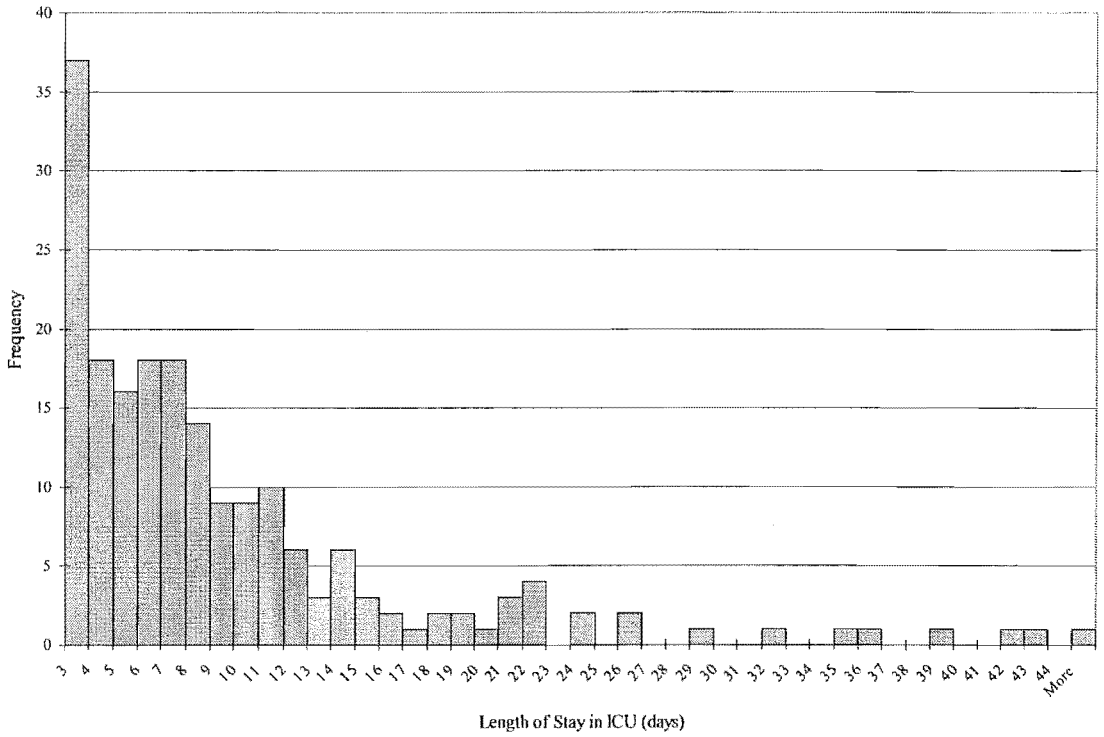


FIGURE 2.1: LENGTH OF STAY OF PATIENTS IN THE CHRISTCHURCH HOSPITAL ICU

Patients with a length of stay in the ICU of less than 72 hours were excluded because in Van den Berghe et al's study (2001; 2003) mortality increased significantly in patients that were in the ICU for greater than five days compared to patients with less than a five day stay (20.2% compared to 1.8% for the conventional treatment group). Mortality for those with tight glucose control did not begin to diverge from those without tight control in Van den Berghe et al's (2001; 2003) study until 3 days, and hence the cut-off chosen here. As only patients with a stay greater than 3 days were recorded, this comparison was not able to be made with the Christchurch Hospital ICU patient population, however it was found that there was no significant difference between patients with 3-5 days stay and patients with greater than 5 days stay (14.5% compared to 13.7%). There was also no correlation between length of stay and APACHE II scores, as seen in Figure 2.2.

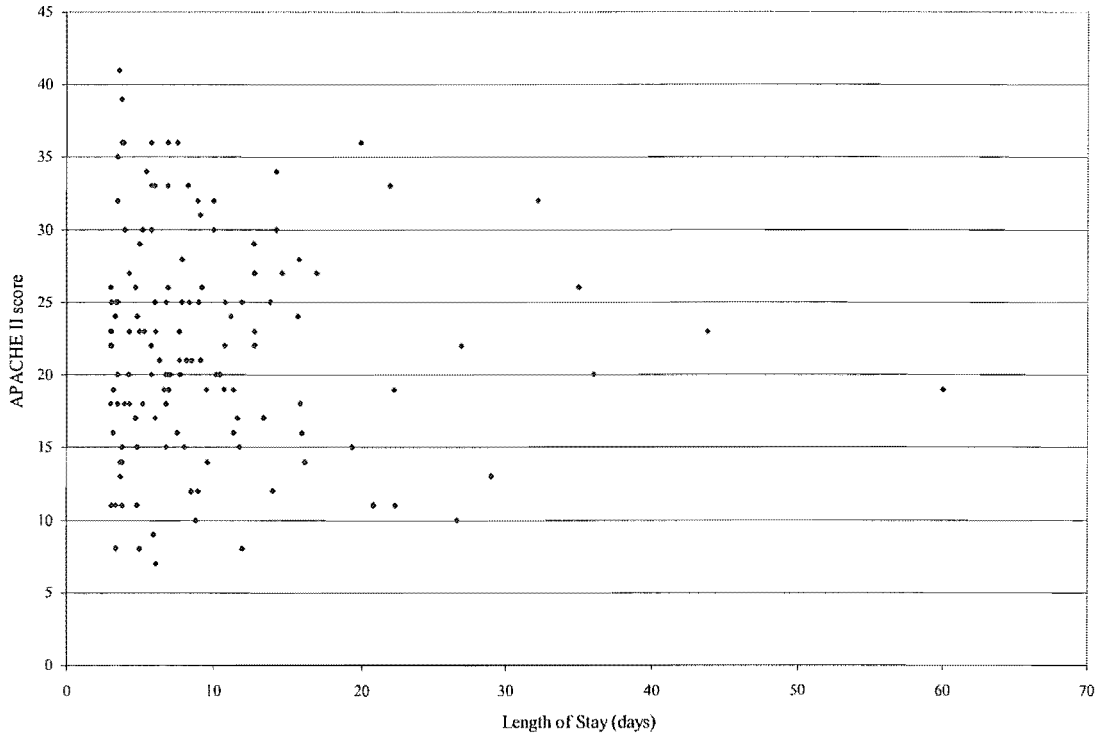


FIGURE 2.2: LENGTH OF STAY VS. APACHE II SCORES IN CHRISTCHURCH HOSPITAL ICU

### *2.2.5 APACHE II Distribution*

The distribution of the 144 APACHE II scores calculated is shown in Figure 2.3, along with the associated risk of death (ROD) in each category. The APACHE II score is based on 12 routinely measured medical variables and predicts the severity of illness in critically ill patients. The calculation of the score is divided into two segments. The first is a physiology score representing the degree of acute illness based on the worst physiological values incurred in the patient during the first 24 hours in the ICU. The second is a preadmission health evaluation indicating health status before acute illness. The score is a value between 0 – 71, with a positive correlation between severity and APACHE II score

(Knaus, et al., 1985). Figure 2.3 shows a relatively normal distribution of APACHE II scores with 26% of patients studied having an APACHE II score in the range of 20 – 24.

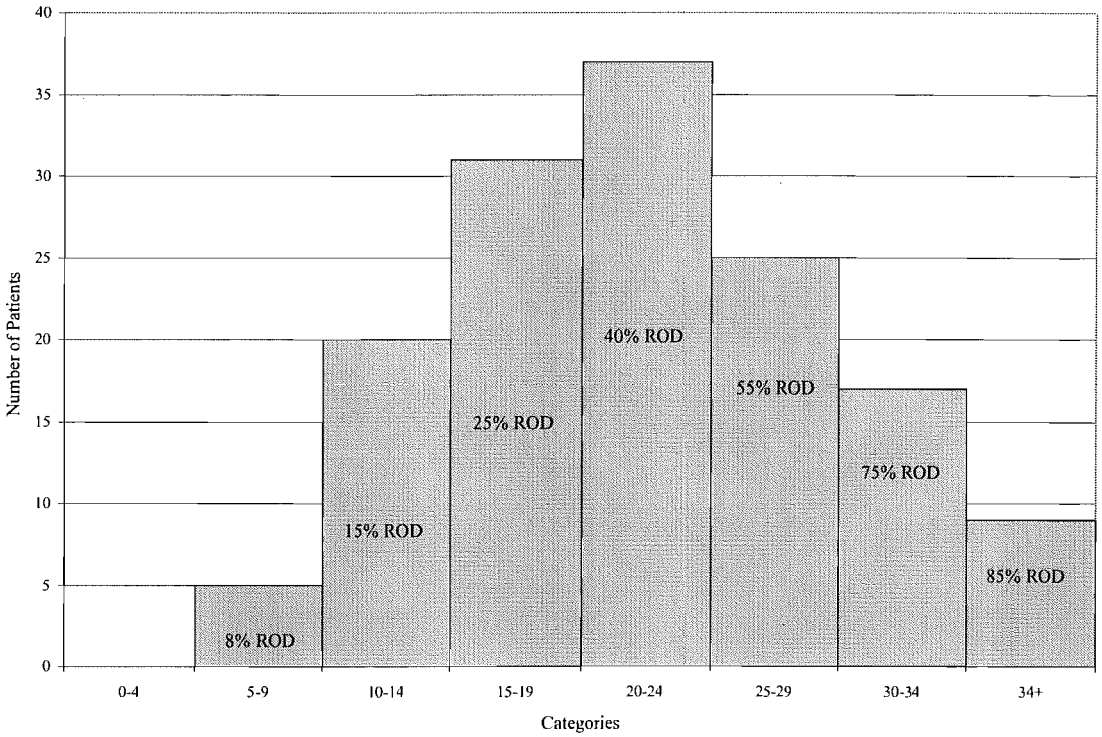


FIGURE 2.3: DISTRIBUTION OF APACHE II SCORES IN CHRISTCHURCH HOSPITAL ICU

### *2.2.6 Effect of Gender*

Gender has no significant effect on mortality when compared across APACHE II categories, as shown by the high *P* values in Table 2.4. Intuitively, the *P* value shown is the probability of "similarity" in mortality between males and females in each APACHE II score category. Survival rates decreased as APACHE II scores increased and there was an 87% survival rate across the 201 patients, as noted in both Table 2.3 and Table 2.4.

TABLE 2.4: EFFECT OF GENDER ON SURVIVAL IN CHRISTCHURCH HOSPITAL ICU

| APACHE II | Assoc. ROD | Total | | Female | | Male | | *P* value |
|---|---|---|---|---|---|---|---|---|
| | | No of Patients | Survival (%) | No of Patients | Survival (%) | No of Patients | Survival (%) | |
| 0-14 | ~4-15% | 25 | 96% | 7 | 100% | 18 | 94% | 1.00 |
| 15-24 | ~25-40% | 68 | 88% | 30 | 90% | 38 | 87% | 1.00 |
| 25+ | ~55-85% | 51 | 80% | 21 | 76% | 30 | 83% | 0.72 |
| Excluded | | 57 | 86% | 20 | 85% | 37 | 86% | 1.00 |
| **TOTAL** | | **201** | **87%** | **78** | **86%** | **123** | **87%** | **0.83** |

### *2.2.7 Survivors and Non-Survivors*

Survivors were compared with non-survivors for each subgroup, and across the entire cohort, with the results shown in Table 2.5. There was no significant difference in age, APACHE II score, length of stay or mechanical ventilation rate between survivors and non-survivors using the $P < 0.05$ statistical significance value. Generally, there was a trend towards younger survivors in the cardiac ($P = 0.15$) and pulmonary ($P = 0.13$) groups, as well as across all categories ($P = 0.13$). Survivors also tended to have a lower APACHE II score across all categories ($P = 0.09$). To better confirm significance in these subgroups, a larger cohort would be required.

TABLE 2.5: PATIENT PARAMETERS IN SURVIVORS AND NON-SURVIVORS IN CHRISTCHURCH HOSPITAL ICU

| Subgroup | No of patients | Age (years) | APACHE II | Mech. Vent | LOS (days) |
|---|---|---|---|---|---|
| All | | | | | |
| Non-survivors | 27 | 56.3 (10 – 82) | 25.4 (7 – 41) | 74% | 11.3 (3.1 – 36.0) |
| Survivors | 174 | 54.8 (1 – 85) | 21.4 (8 – 36) | 66% | 9.8 (3.0 – 60.0) |
| Cardiac | | | | | |
| Non-survivors | 2 | 57.5 (55 – 60) | 31.0 (23 – 39) | 100% | 3.5 (3.1 – 3.8) |
| Survivors | 30 | 65.8 (30 – 85) | 21.4 (8 – 36) | 80% | 6.6 (3.0 – 21.8) |
| Pulmonary | | | | | |
| Non-survivors | 10 | 63.7 (24 – 82) | 22.0 (20 – 26) | 50% | 13.0 (4.7 – 36) |
| Survivors | 24 | 57.0 (18 – 79) | 26.5 (15 – 36) | 33% | 10.8 (3.1 – 24.8) |
| Sepsis | | | | | |
| Non-survivors | 1 | 49.0 | 27.0 | 100% | 12.8 |
| Survivors | 14 | 55.9 (1 – 82) | 26.2 (21 – 30) | 57% | 11.9 (3.0 – 39.9) |
| Other Medical | | | | | |
| Non-survivors | 4 | 66.0 (47 - 84 | 27.7 (25 – 33) | 75% | 9.0 (3.4 – 22.3) |
| Survivors | 22 | 52.0 (20 – 84 | 25.2 (17 – 36) | 50% | 10.8 (3.0 – 35.0) |
| Neurologic | | | | | |
| Non-survivors | 3 | 64.3 (53 – 78) | 15.7 (7 – 20) | 67% | 5.6 (3.5 – 7.1) |
| Survivors | 16 | 52.1 (1 – 81) | 18.7 (11 – 24) | 75% | 9.1 (3.2 – 43.8) |
| General Surgical | | | | | |
| Non-survivors | 5 | 69.2 (59 – 77) | 27.0 (18 – 41) | 80% | 16.1 (3.6 – 32.2) |
| Survivors | 36 | 63.9 (17 – 85) | 20.4 (10 – 35) | 67% | 9.8 (3.0 – 42.5) |
| Trauma | | | | | |
| Non-survivors | 2 | 23.0 (20 – 26) | 25.0 | 100% | 6.5 (4.5 – 8.4) |
| Survivors | 32 | 35.2 (15 – 83) | 16.8 (8 – 30) | 84% | 11.0 (3.0 – 60.0) |

Age, APACHE II score and LOS are expressed as 'mean (range)'

## 2.3 EFFECT OF BLOOD GLUCOSE LEVELS

Determining the level of blood glucose and its effect on mortality was the primary objective of this retrospective data audit. However, upon observation of the data, it was found that glucose measurement was often far less frequent than ideal, with multiple days with no glucose values recorded for a number of patients. ICU protocol suggests that a patient's blood glucose levels should be measured, at minimum, every four hours, and more frequently when blood glucose levels are in a hyper- or hypoglycemic range. The glucose values recorded had varying sample-times within a patient's stay, thus reducing the ease with which a statistically valid mean glucose value could be calculated.

Of 3652 blood glucose measurements over all patients, the majority (34%) were in the 6 - 8 mmol/L category, as shown in Figure 2.4. There were also 116 (3%) hypoglycemic values recorded by 81 patients, as shown in Figure 2.4 and Figure 2.5. In this case, the hypoglycemic threshold is set at 4 mmol/L for these hyperglycemic patients, representing a significant drop from their elevated glucose level. Figure 2.5 shows that 38 patients (19%) had at least one blood glucose reading greater than 15 mmol/L and that of these patients, 13 (6%) had at least one blood glucose reading greater than 20 mmol/L. These values show that the blood glucose control in the Christchurch Hospital ICU is less than ideal.

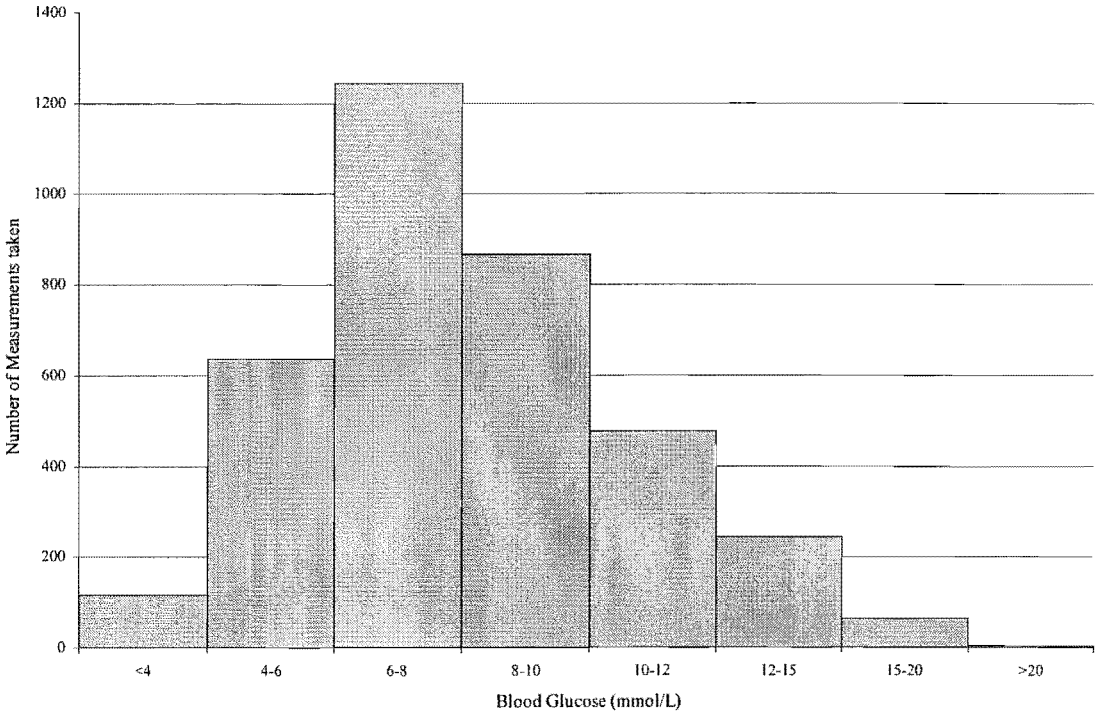


FIGURE 2.4: TOTAL BLOOD GLUCOSE MEASUREMENTS OBTAINED IN THE CHRISTCHURCH HOSPITAL ICU ACROSS ALL PATIENTS

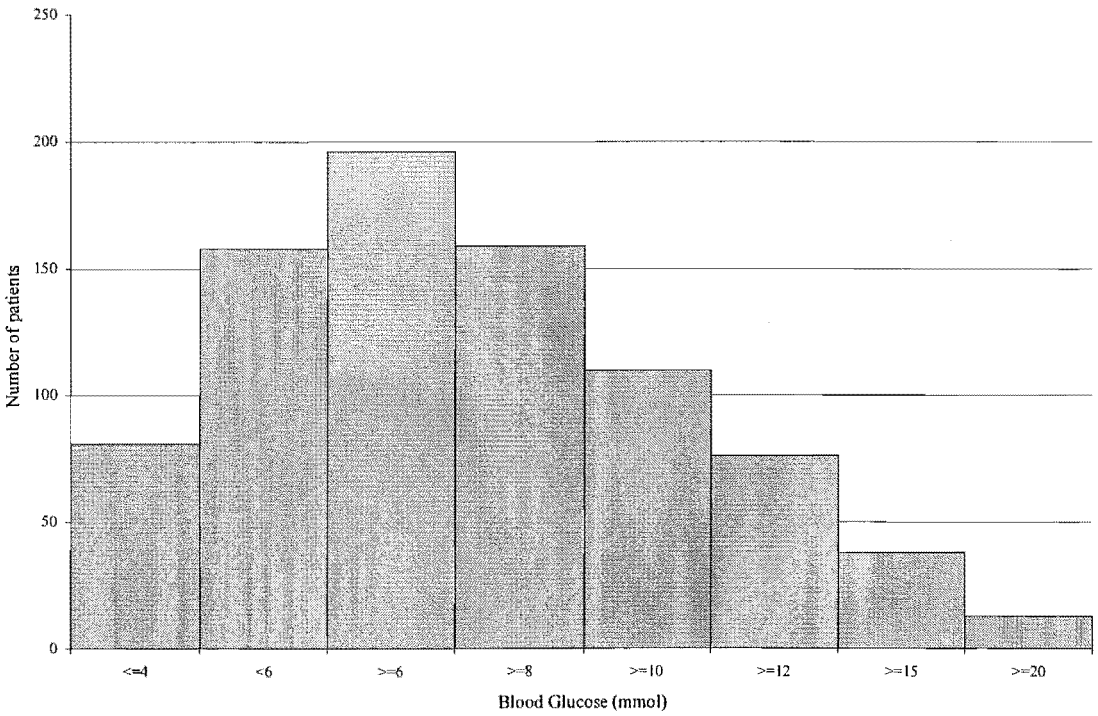


FIGURE 2.5: NUMBER OF CHRISTCHURCH HOSPITAL ICU PATIENTS WITH AT LEAST ONE READING IN A GIVEN BLOOD GLUCOSE CATEGORY

Table 2.6 shows the measurement frequency, maximum and range of blood glucose values within the patient categories and overall. The number of measurements per day is an average value obtained by dividing the total number of blood glucose measurements by the length of stay. The maximum blood glucose value is the highest recorded blood glucose value, and the range is the difference between the highest and lowest recorded blood glucose values. The number of measurements per day was higher in non-survivors ($P$ = 0.03), suggesting the frequency of blood glucose measurement was associated with patients with a higher risk of death. The reason for this result is probably that Christchurch Hospital ICU protocol recommends that blood glucose should be measured more frequently at hyperglycemic levels. Interestingly, the protocol that suggests blood glucose levels be measured every 4 hours (6 times per day) has not been followed in many patients, as shown by the average number of measurements per day in Table 2.6.

The maximum value of blood glucose along with the range of blood glucose values was higher in non-survivors ($P$ = 0.001 and $P$ = 0.003, respectively), suggesting that the level of deviation from basal blood glucose values has a negative impact on survival in critically ill patients, especially in trauma patients ($P$ = 0.04 and $P$ = 0.05, respectively). The maximum values of blood glucose correlate well with those found at Stamford Hospital ICU for both survivors (10.8 mmol/L compared to 9.8 mmol/L) and non-survivors (14.1 mmol/L compared to 14.3 mmol/L). This finding suggests that limiting the maximum and range of blood glucose, and hence the level of deviation, may be more important in the clinical situation.

TABLE 2.6: EFFECT OF FREQUENCY, MAXIMUM AND RANGE OF BLOOD GLUCOSE MEASUREMENTS ON SURVIVAL IN CHRISTCHURCH HOSPITAL ICU

| Subgroup | No of patients | Number of Measurements per day | Maximum Blood Glucose (mmol/L) | Blood Glucose Range (mmol/L) |
|---|---|---|---|---|
| All | | | | |
| Non-survivors | 27 | 4.7 (0.2 – 13.0) | 14.1 (7.1 – 22.2) | 8.4 (1.5 – 15.7) |
| Survivors | 174 | 3.1 (0.1 – 16.2) | 10.8 (3.9 – 28.9) | 6.1 (0 – 26.7) |
| Cardiac | | | | |
| Non-survivors | 2 | 10.3 (8.8 – 11.9) | 15.9 (14.7 – 17.1) | 12.6 (9.7 – 15.4) |
| Survivors | 30 | 4.4 (0.2 – 9.6) | 12.1 (8.2 – 19.8) | 7.6 (2.2 – 16.0) |
| Pulmonary | | | | |
| Non-survivors | 10 | 4.3 (0.4 – 8.0) | 12.0 (6.9 – 18.3) | 7.8 (1.5 – 13.3) |
| Survivors | 24 | 3.2 (0.1 – 7.9) | 11.1 (6.0 – 17.6) | 6.5 (0.0 – 14.8) |
| Sepsis | | | | |
| Non-survivors | 1 | 7.2 | 11.5 | 9.7 |
| Survivors | 14 | 3.5 (0.1 – 8.0) | 11.5 (4.6 – 17.6) | 7.4 (0.0 – 14.3) |
| Other Medical | | | | |
| Non-survivors | 4 | 7.9 (1.4 – 13.0) | 16.6 (12.9 – 22.2) | 12.0 (8.1 – 16.7) |
| Survivors | 22 | 4.7 (0.1 – 11.2) | 14.3 (6.0 – 28.9) | 9.5 (0.0 – 26.7) |
| Neurologic | | | | |
| Non-survivors | 3 | 4.4 (0.5 – 7.2) | 13.7 (7.2 – 18.4) | 6.5 (1.7 – 11.7) |
| Survivors | 16 | 2.4 (0.1 – 10.0) | 9.2 (3.6 – (18.4) | 3.9 (0.0 – 14.3) |
| General Surgical | | | | |
| Non-survivors | 5 | 2.0 (0.2 – 5.0) | 11.1 (7.8 – 13.8) | 6.4 (3.0 - 10.1) |
| Survivors | 36 | 2.7 (0.1 – 10.3) | 10.0 (5.4 – 18.9) | 5.4 (0.0 – 14.7) |
| Trauma | | | | |
| Non-survivors | 2 | 0.6 (0.6 – 0.7) | 13.9 (12.4 – 15.4) | 7.4 (5.1 – 9.7) |
| Survivors | 32 | 1.2 (0.1 – 16.2) | 8.3 (4.5 – 16.6) | 3.1 (0.0 – 13.9) |

#/day, maximum and range are expressed as 'mean (range)'

### *2.3.1 Calculating the Blood Glucose Mean*

Calculation of mean blood glucose values for this irregularly sampled data required the use of the trapezoidal rule together with a random walk model to bridge the gaps between data so that confidence intervals can be determined for the means.

*Method for Determining Trapezoidal Mean*

Let $x_1, \ldots, x_m$ be the blood glucose measurements, in mmol/L, recorded at times $t_1, \ldots, t_m$, in hours. Set $t_1 = 0$, $t_m = T$, and $\tau$ to the smallest time interval between measurements across all patients, which in this case is one hour. The length of the data is expressed by $n$ in terms of $\tau$, $n = T/\tau$, and the length of the intervals between each measurement is defined

$$c_i = \frac{t_{i+1} - t_i}{\tau} \quad \text{for } i = 1 \text{ to } m\text{-}1 \tag{2.1}$$

The parameters $c_i$, $t_i$, $x_i$ and $\tau$ are shown schematically in Figure 2.6, which shows a series of blood glucose measurements with different sample times. When a linear line joins the points, as shown for the values $x_1, \ldots, x_9$, the area under the graph divided by the length of the series, $T$, is the trapezoidal mean. The nomenclature renames the measurements, time and sample times using $x_i$, $t_i$ and $c_i$, respectively.

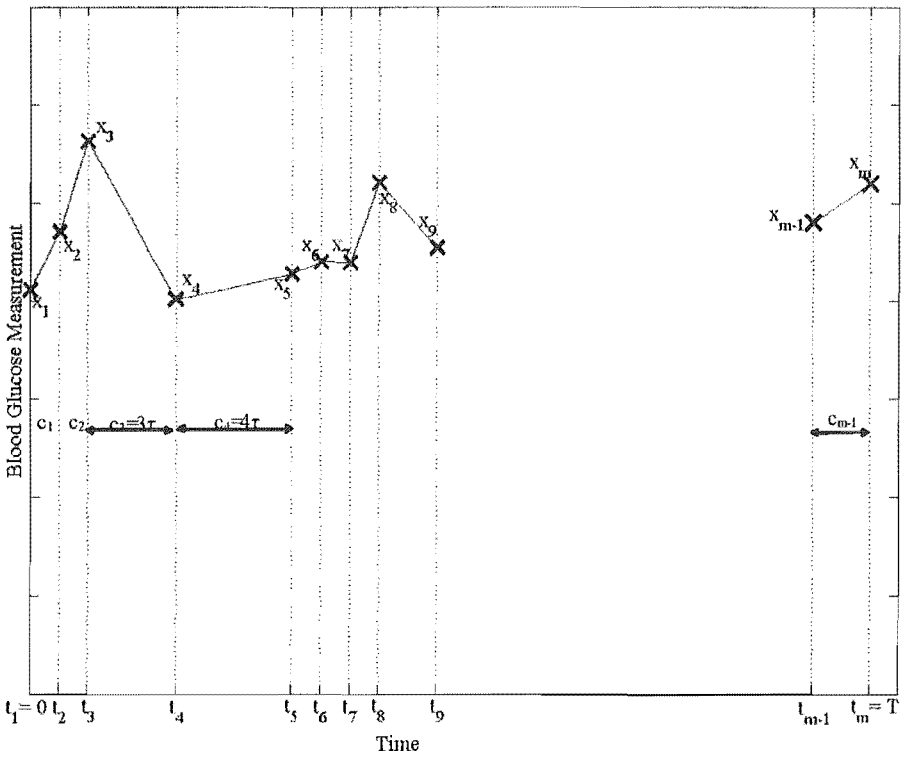


FIGURE 2.6: TRAPEZOIDAL MEAN CALCULATION NOMENCLATURE

Assuming that the blood glucose readings are ergodic, and using the trapezoidal rule as shown in Figure 2.6, an estimate of the patient's mean blood glucose for the duration $[0,T]$ is defined (Burden and Faires, 1989):

$$\hat{\mu}_x = \frac{1}{T}\int_0^T x(t)dt \approx \frac{1}{T}\sum_{i=1}^{m-1}\frac{c_i\tau}{2}(x_i + x_{i+1}) = \frac{1}{2n}\left[c_1x_1 + \sum_{i=2}^{m-1}(c_{i-1} + c_i)x_i + c_{m-1}x_m\right] \quad (2.2)$$

*Method for determining Mean Confidence Intervals*

Using the method described for determining the trapezoidal mean for the data, it is assumed that if blood glucose had been measured between two measured points, then it would lie on the linear line between those two points. However, this assumption may not hold. Therefore, a method for estimating the range within which this imaginary blood glucose measurement lies is required.

As the smallest time interval between measurements is one hour, it will be taken as the new sample time. A measurement gap occurs whenever the length of the measurement interval is greater than one hour, $c_i > 1$ hour. One way to obtain an estimate for sample times when no measurement was taken is to "bridge" the measurement gaps using an appropriate random process model. Here, because of the sparseness of the data, a random walk constrained to the measurements at both ends will be used, forming a continuous data series between the first and last measurements taken at one hour intervals.

Consider a measurement gap with length $k$, and let $x_0^*$ and $x_k^*$ denote the measurements at the beginning and end of the gap. For the length of the measurement gap, $i = 0, \ldots, k$, the bridging process is given by

$$x_i^* = z_i - \frac{i}{k}(z_k - x_k^*) \tag{2.3}$$

where the simple random walk, $z_i$, starts from $x_0^*$ and takes random steps $w_1, w_2, \ldots w_k$

$$z_i = x_0^* + \sum_{j=1}^{i} w_j \tag{2.4}$$

Thus, the bridging process is a modification of the simple random walk so that the constraints at the ends are met. The bridging process can be expressed directly in terms of $w_i$:

$$x_i^* = \left(\frac{k-i}{k}\right)x_0^* + \left(\frac{i}{k}\right)x_k^* + \left(\frac{k-i}{k}\right)\sum_{j=1}^{i} w_j - \left(\frac{i}{k}\right)\sum_{j=i+1}^{k} w_j \tag{2.5}$$

where $x_i^*$ is a simple linear interpolation of the end-points, $x_0^*$ and $x_k^*$, perturbed by a weighted sum of $w_1,\ldots,w_k$.

To complete the definition of the bridging process, an appropriate distribution must be selected for randomly determining the $w_i$ values. Since these weighted sum values are independent and identically distributed, a convenient choice would be a distribution that results in $x_i^*$ also belonging to the same distribution family. Two distributions that fit this description are the Normal distribution and the Cauchy distribution (Evans, et al., 1993). To determine which of these two distributions was a better representation of the data, the differences in blood glucose measurements that were taken one hour apart from all patients are considered. Figure 2.7 shows the differences in blood glucose measurements taken one hour apart across all patients receiving insulin, and are compared to the Normal and Cauchy distributions.

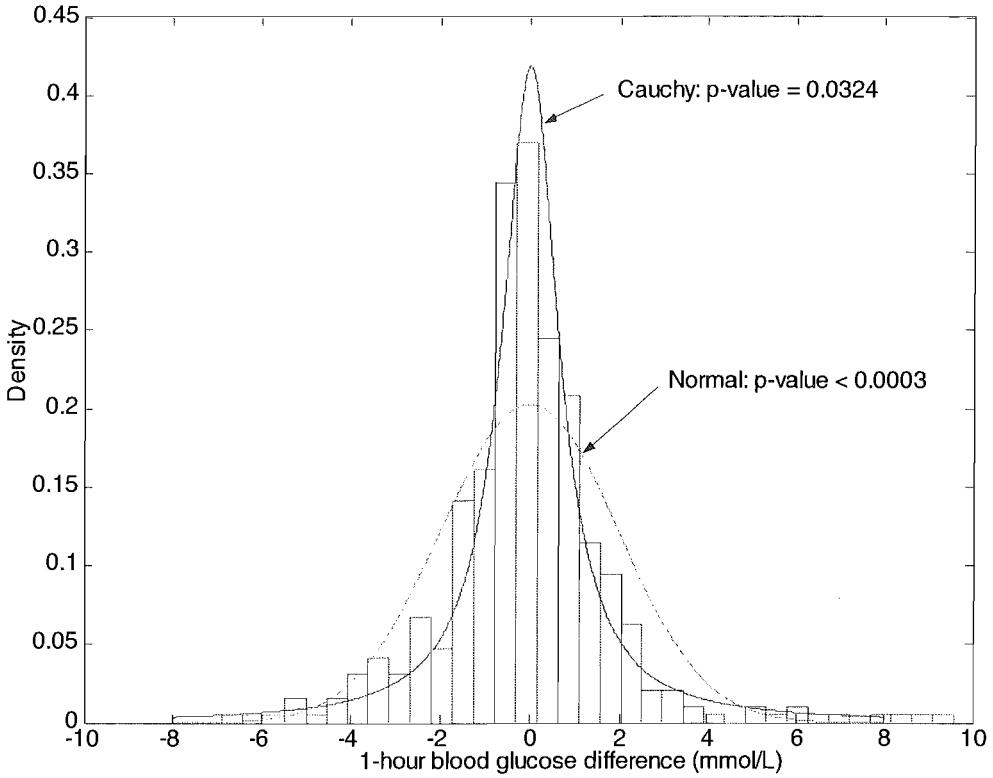


FIGURE 2.7: DIFFERENCES BETWEEN BLOOD GLUCOSE MEASUREMENTS TAKEN ONE HOUR APART

The Cauchy distribution with location 0 and scale, $s^* = 0.76$, provides a better fit than the normal distribution to the data obtained ($P = 0.03$ compared to $P < 0.0003$ using the Kolmogorov-Smirnov goodness-of-fit test). The value of the scale, $s^*$, in the Cauchy distribution was estimated by the maximum likelihood method. The one-hour differences of the bridging process must have a scale that matches $s^*$, since the distribution of the random walk between actual measurements, $x_i$, must match the Cauchy distribution.

$$x_i^* - x_{i-1}^* = \frac{1}{k}(x_k^* - x_0^*) + \left(\frac{k-1}{k}\right)w_i - \frac{1}{k}\sum_{j=1,\ldots,i-1,i+1,\ldots,k} w_j \tag{2.6}$$

$$(x_i^* - x_{i-1}^*) - \frac{1}{k}(x_k^* - x_0^*) \sim \text{Cauchy}(0, s^*) \tag{2.7}$$

If the distribution of the weighted sum values, $w_i$, matches the Cauchy distribution, then the scale, $s^*$, is defined:

$$s^* = \frac{2(k-1)}{k} s_w \tag{2.8}$$

Let $s_i^*$ be the scale of the measurements, $x_i^*$, then using the expression for $x_i^*$ in terms of the weighted sum values, $w_i$, the scale becomes:

$$s_i^* = \frac{2i(k-i)}{k} s_w = \frac{i(k-i)}{(k-1)} s^* \tag{2.9}$$

Therefore, the contribution of this measurement gap to the $(1 - \alpha)\%$ confidence interval for the mean, $\mu_x$, is

$$\delta_k = \frac{q_{\alpha/2}}{n} \sum_{i=1}^{k-1} s_i^* = \frac{q_{\alpha/2} s^*}{n(k-1)} \sum_{i=1}^{k-1} i(k-i) = \frac{q_{\alpha/2} s^* k(k+1)}{6n} \tag{2.10}$$

where $q_{\alpha/2}$ is the $(\alpha/2)$-quantile of the Cauchy (0, 1) distribution. For example, to achieve a 90 % confidence interval, $q_{0.05} = 6.314$. If there are $M$ measurement gaps of lengths, $k_1,\ldots,k_M$, , then an approximate $(1 - \alpha)\%$ confidence interval for the mean, $\mu_x$ is

$$\left[ \hat{\mu}_x - \sum_{i=1}^{M} \delta_{k_i}, \hat{\mu}_x + \sum_{i=1}^{M} \delta_{k_i} \right] \tag{2.11}$$

In summary, the blood glucose mean is determined using Equation (2.2) with a 90% confidence interval determined using Equation (2.11).

### *2.3.2 Blood Glucose Mean Values*

Similar studies (Krinsley, 2003) do not explain their method for calculating the mean blood glucose level, and may have calculated simple mean values. This method only gives a true representation of the mean when the sampling interval is constant for all measurements. Krinsley (2003) mentions that the number of glucose values obtained for each patient correlated significantly with the patients length of stay ($R = 0.870$, $P < 0.001$), and hence it is assumed that the samples taken have a relatively consistent sampling time. However, in the case of samples obtained by medical staff at the Christchurch Hospital ICU, the sampling time was definitely not consistent and hence the method of using trapezoidal means was devised.

The trapezoidal means were calculated using Equation (2.2) for the subset of 86 patients that were on insulin at any stage during their stay. This subset was chosen as they were most likely to have a greater density of data. Table 2.7 shows the effect of the mean blood glucose, estimated by the trapezoidal mean on survival in each of the patient sub-groups of those patients on insulin. Overall, the mean blood glucose was higher in non-survivors than in survivors ($P = 0.014$). This result was also the case in cardiac patients ($P = 0.016$). Insufficient data is likely the reason that mean blood glucose values were not significantly higher in the other subgroups.

TABLE 2.7: EFFECT OF BLOOD GLUCOSE TRAPEZOIDAL MEANS OF PATIENTS ON INSULIN ON SURVIVAL IN CHRISTCHURCH HOSPITAL ICU

| Subgroup | No of patients | Trapezoidal Mean Blood Glucose (mmol/L) |
|---|---|---|
| All | | |
| Non-survivors | 16 | 9.3 (6.5 – 14.1) |
| Survivors | 70 | 7.9 (4.5 – 12.2) |
| Cardiac | | |
| Non-survivors | 2 | 9.8 (9.5 – 10.1) |
| Survivors | 12 | 7.5 (5.9 – 9.9) |
| Pulmonary | | |
| Non-survivors | 6 | 8.0 (7.0 – 9.9) |
| Survivors | 12 | 7.6 (4.9 – 9.6) |
| Sepsis | | |
| Non-survivors | 1 | 7.4 |
| Survivors | 8 | 8.2 (6.1 – 10.0) |
| Other Medical | | |
| Non-survivors | 3 | 10.7 (6.5 – 14.1) |
| Survivors | 13 | 8.4 (6.9 – 10.9) |
| Neurologic | | |
| Non-survivors | 2 | 11.6 (10.2 – 13.0) |
| Survivors | 4 | 9.1 (7.2 – 12.2) |
| General Surgical | | |
| Non-survivors | 2 | 9.0 (8.1 – 9.9) |
| Survivors | 11 | 7.5 (4.5 – 9.8) |
| Trauma | | |
| Non-survivors | - | - |
| Survivors | 1 | 9.7 |

### *2.3.3 Effect of Blood Glucose on Mortality*

Table 2.6 shows that the maximum and range of blood glucose levels are higher in non-survivors than in survivors ($P = 0.001$ and $P = 0.003$, respectively), however it does not show the relationship between the values obtained and survival. Table 2.7 shows that a higher mean value is also correlated with mortality ($P = 0.014$). The retrospective design of this study prevents conclusions about if a higher maximum, range or mean blood glucose value causes a decreased survival rate, or is just a marker of decreased survival. However, from Van den Berghe et al's (2001; 2003) study, the assumption that elevated blood glucose may be the cause can be assumed. Even if the relationship is not causal, past studies (Krinsley, 2003; Van den Berghe, et al., 2001; 2003) and the results from this study of the Christchurch Hospital ICU show that there is a strong association between glucose levels and mortality that should not be ignored.

Table 2.8 shows the effect of the maximum recorded blood glucose level on survival for 201 patients from the Christchurch Hospital ICU. Patients with a highest recorded blood glucose value less than 6 mmol/L had the highest survival rate. Using the protocol set by Christchurch Hospital, those patients with a maximum recorded blood glucose in the range of 6 – 8 mmol/L, had a reduced survival rate compared with those in the less than 6 mmol/L category. The trend shows that as the maximum blood glucose increases, the chance of ICU survival decreases, as shown in Figure 2.8. Note that the low patient numbers in the categories 18 – 20 mmol/L and >20 mmol/L, although shown on the graph, have not been included in the trend line calculation. With a larger cohort, these values

may follow the trend more closely, although, the 18 – 20 mmol/L value lies almost on the trend line.

TABLE 2.8: MAXIMUM BLOOD GLUCOSE VALUE AND ICU SURVIVAL IN CHRISTCHURCH HOSPITAL ICU

| Maximum Blood Glucose (mmol/L) | No. of Patients | Survival (%) |
|---|---|---|
| <6 | 14 | 100% |
| 6-8 | 37 | 92% |
| 8-10 | 48 | 96% |
| 10-12 | 34 | 85% |
| 12-14 | 20 | 70% |
| 14-16 | 27 | 78% |
| 16-18 | 9 | 78% |
| 18-20 | 6 | 67% |
| >20 | 6 | 83% |

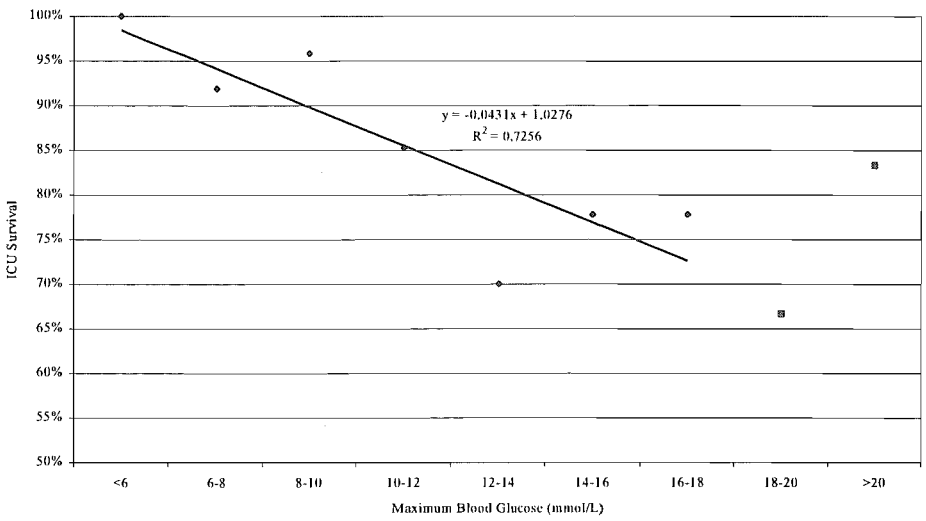


FIGURE 2.8: MAXIMUM BLOOD GLUCOSE VS ICU SURVIVAL IN CHRISTCHURCH HOSPITAL ICU

Similar trends were seen for the range and trapezoidal mean of blood glucose, as shown in Table 2.9 and 2.10. If the range of greater than 20 mmol/L is disregarded due to insufficient data, then the highest survival rate is 96% in patients with a blood glucose range of less than 5 mmol/L. The survival rate decreased 21% if the patient's blood glucose range was 5-10 mmol/L. Similarly, the survival rate decreased 12% if the trapezoidal mean was in the 6 – 7 mmol/L category compared to the <6 mmol/L category. The trend shows that as the trapezoidal blood glucose mean increases, the chance of ICU survival decreases, as shown in Figure 2.9. Although shown on the graph, the lumped together 10+ mmol/L category has not been included in the trend line calculation due to its low patient population and potentially extreme result. Alternatively, the trend may not be linear.

TABLE 2.9: BLOOD GLUCOSE RANGE AND ICU SURVIVAL IN CHRISTCHURCH HOSPITAL ICU

| Blood Glucose Range (mmol/L) | No. of Patients | Survival (%) |
|---|---|---|
| <5 | 90 | 96% |
| 5-10 | 63 | 76% |
| 10-15 | 36 | 83% |
| 15-20 | 5 | 60% |
| >20 | 3 | 100% |

TABLE 2.10: BLOOD GLUCOSE TRAPEZOIDAL MEAN AND ICU SURVIVAL IN CHRISTCHURCH HOSPITAL ICU

| Blood Glucose Trapezoidal Mean (mmol/L) | No. of Patients | Survival (%) |
|---|---|---|
| <6 | 4 | 100% |
| 6-7 | 16 | 88% |
| 7-8 | 32 | 88% |
| 8-9 | 10 | 80% |
| 9-10 | 19 | 84% |
| 10+ | 7 | 29% |

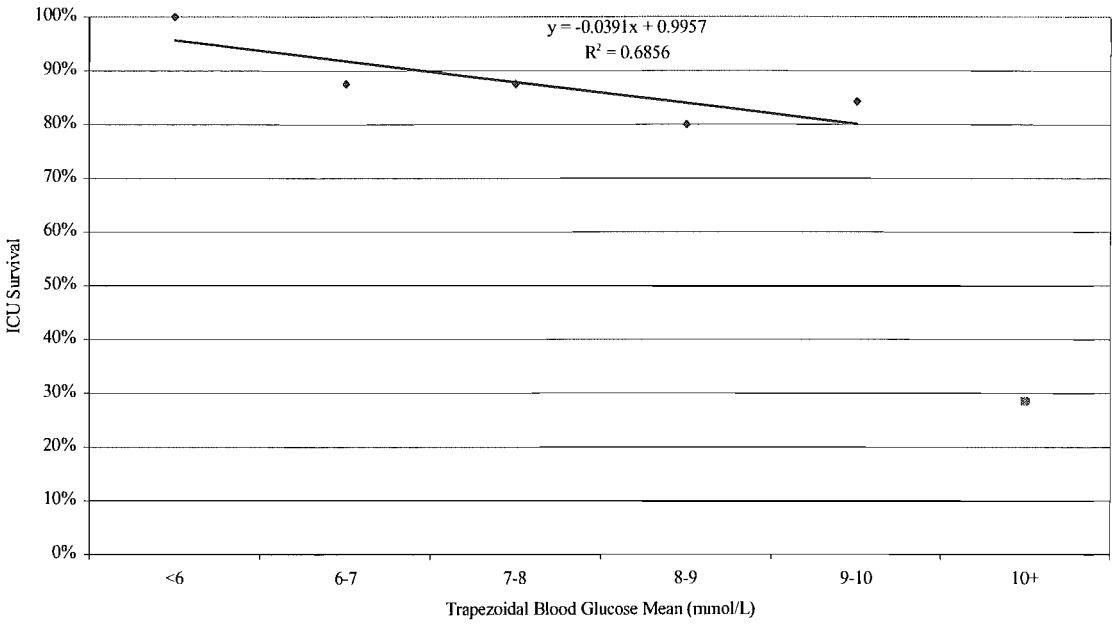


FIGURE 2.9: TRAPEZOIDAL BLOOD GLUCOSE MEAN VALUES VS ICU SURVIVAL IN CHRISTCHURCH HOSPITAL ICU

### *2.3.4 Effect of Blood Glucose Measurement Intervals on Mean Calculation*

To put the mean glucose values into context, confidence intervals were calculated. However, it was found that the length of the intervals was far too long to be helpful, due to the scarcity of the data gathered. The effect of the time periods between measurements was then considered, and by plotting the half-width of the confidence intervals against the average period between blood glucose measurements, as shown in Figure 2.10, a largely linear relationship was found. The linear least squares fit shown in Figure 2.10 considers only patients with a half-width less than 6 mmol/L, and consequently a confidence interval length of less than 12 mmol/L. This 12 mmol/L value represents an extreme size for a confidence interval and would render the associated mean value useless.

Using this relationship, researchers such as Van den Berghe et al (2001; 2003) who measure up to every four hours, may have uncertainty on their actual glucose value of up to 4.68 mmol/L. This result means that patients in the controlled group, with mean glucose levels between 4.4 and 6.1 mmol/L, could actually have significantly more variable and higher mean glucose levels. Table 2.11 shows selected values from Figure 2.10. The potential variation of blood glucose with infrequent sampling makes a strong case for more regular measurements and the use of emerging blood glucose sensors in measuring and regulating blood glucose levels.

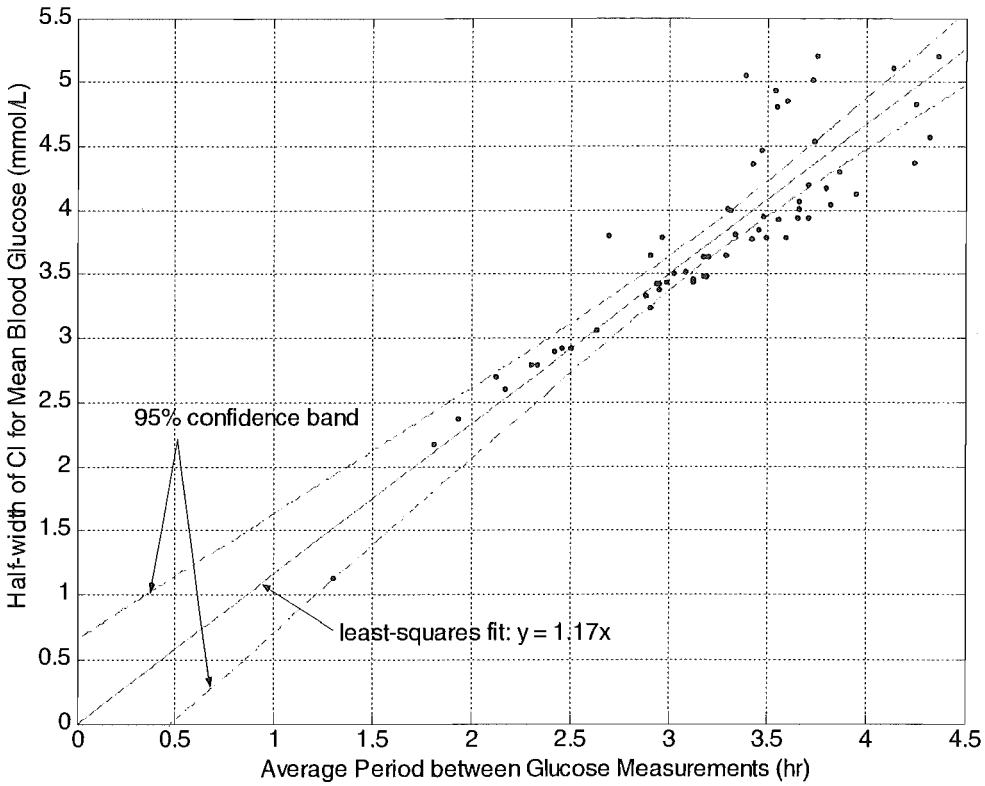


FIGURE 2.10: AVERAGE PERIOD BETWEEN BLOOD GLUCOSE MEASUREMENTS VS CONFIDENCE INTERVAL HALF-WIDTH

TABLE 2.11: AVERAGE PERIOD BETWEEN BLOOD GLUCOSE MEASUREMENTS VS CONFIDENCE INTERVAL HALF-WIDTH

| Average Period between Blood Glucose Measurements (hrs) | Certainty on Measurement (mmol/L) |
|---|---|
| 0.5 | ± 0.59 |
| 1 | ± 1.17 |
| 2 | ± 2.34 |
| 3 | ± 3.51 |
| 4 | ± 4.68 |
| 5 | ± 5.85 |
| 6 | ± 7.02 |

## 2.4 EFFECT OF BLOOD INSULIN LEVELS

It is debated (Annane and Melchior, 2003; Van den Berghe, et al., 2001; 2003) whether it is the insulin infused or the tight management of blood glucose levels that leads to the reduction in mortality in critically ill patients. Hence, the average insulin infused per hour and the proportion of the patient's stay that they were receiving an insulin infusion were calculated to test the theory proposed by Annane and Melchior (2003) that it is the insulin infused, and not the lowered blood glucose values, that resulted in a lowered risk of mortality.

When survivors are compared to non-survivors there is a negative correlation between average insulin infused and survival ($P = 0.01$) over all patients. More specifically, non-survivors received more insulin on average than survivors. As the size of the patients subsets was small, it is feasible that there was a correlation overall, yet not within any of the subsets.

Results were the same for the proportion of stay that a patient was on insulin, with the non-survivors on insulin for a longer period during their stay ($P = 0.02$). These results confirm the findings of Van den Berghe et al (2003) that there is a negative relationship between insulin infused and survival rate.

TABLE 2.12: EFFECT OF INSULIN INFUSION ON SURVIVAL IN CHRISTCHURCH HOSPITAL ICU

| Subgroup | No of patients | Average Insulin Infused (U/hr) | Proportion of Stay on Insulin |
|---|---|---|---|
| All | | | |
| Non-survivors | 27 | 1.1 (0 – 5.7) | 41% (0 – 97) |
| Survivors | 174 | 0.5 (0 – 5.7) | 24% (0 – 98) |
| Cardiac | | | |
| Non-survivors | 2 | 3.6 (3.4 – 3.8) | 90% (84 – 97) |
| Survivors | 30 | 0.8 (0 – 3.7) | 41% (0 – 98) |
| Pulmonary | | | |
| Non-survivors | 10 | 0.7 (0 – 2.1) | 41% (0 – 79) |
| Survivors | 24 | 0.4 (0 – 2.4) | 27% (0 – 94) |
| Sepsis | | | |
| Non-survivors | 1 | 1.2 | 89% |
| Survivors | 14 | 0.5 (0 – 1.9) | 27% (0 – 83) |
| Other Medical | | | |
| Non-survivors | 4 | 2.6 (0 – 5.7) | 67% (0 – 93) |
| Survivors | 22 | 1.0 (0 – 5.7) | 43% (0 – 97) |
| Neurologic | | | |
| Non-survivors | 3 | 1.0 (0 – 1.8) | 45% (0 – 74) |
| Survivors | 16 | 0.4 (0 – 3.2) | 16% (0 – 90) |
| General Surgical | | | |
| Non-survivors | 5 | 0.2 (0 – 1.0) | 13% (0 – 61) |
| Survivors | 36 | 0.3 (0 – 1.9) | 17% (0 – 90) |
| Trauma | | | |
| Non-survivors | 2 | 0.0 | 0% |
| Survivors | 32 | 0.1 (0 – 1.6) | 2% (0 – 47) |

## 2.5 SUMMARY

This chapter analysed data from 201 patients that had a length of stay of greater than 72 hours in the Christchurch Hospital ICU over a 1 year period. The proportion of patients in each subset was found to be similar to that of the Stamford Hospital ICU (Krinsley, 2003), but unlike that studied by Van den Berghe et al (2001; 2003) whose population was mainly cardiac patients.

Unlike Van den Berghe et al (2001; 2003), the mortality and APACHE II scores did not seem to increase with length of stay. However, it is suspected that if all patients (rather than just those with a length of stay of 72 hours or more) were considered that this phenomenon may appear. It might also be due to the different patient cohorts. There was no significant difference in age, APACHE II score, length of stay or mechanical ventilation rates between survivors and non-survivors.

The number of measurements per day was higher in non-survivors ($P = 0.03$), as was the maximum value of blood glucose and the range of blood glucose values ($P = 0.001$ and $P = 0.003$, respectively), especially in trauma patients ($P = 0.04$ and $P = 0.05$, respectively). The trapezoidal mean of blood glucose, calculated in 86 patients who received insulin therapy at any time was higher among non-survivors than survivors ($P = 0.014$). Insulin infusion averages and proportion of stay were negatively correlated with mortality ($P = 0.01$ and $P = 0.02$, respectively), confirming findings by Van den Berghe et al (2003).

The general trend was that survival decreased with increasing maximum blood glucose, range of blood glucose and trapezoidal mean of blood glucose, suggesting that these three parameters have a negative effect on the survival of an ICU patient. From the data presented, it is proposed that the maximum blood glucose level, and hence the range of blood glucose levels, may be the factor most detrimental to a patients ICU survival. However, further studies on a larger patient cohort would be required to prove this idea.

The effect of the length of time between blood glucose measurements was considered, and it was found that the error in the mean blood glucose calculated increased linearly with time. Standard practice of measurements every four hours, such as outlined by the Christchurch Hospital ICU and Van den Berghe et al (2001; 2003) may not be appropriate for controlling glucose levels due to the large errors involved. This result further reiterates the use of glucose sensing technology and automated insulin infusion in critical care environments.

Overall, it was found that the Christchurch Hospital ICU has sub-optimal management of blood glucose levels, both by Van den Berghe et al's (2001; 2003) protocol and their own. Hence, the aim of the entire project, to develop an automated infusion system for tight glucose control in critically ill patients, is justified by the findings of this retrospective data audit.

## 2.6 REFERENCES

Annane, D. and Melchior, J. C. 2003. Hormone Replacement Therapy for the Critically Ill. *Crit Care Med.* 31(2): 634-635

Bistrian, B. R. 2001. Hyperglycemia and Infection: Which Is the Chicken and Which Is the Egg? *JPEN J Parenter Enteral Nutr.* 25(4): 180-181

Bloomgarden, Z. T. 2003. Inflammation and Insulin Resistance. *Diabetes Care.* 26(6): 1922-1926

Burden, R. and Faires, J. (1989). *Numerical Analysis*: PWS-KENT Publishing Company.

Capes, S. E., Hunt, D., Malmberg, K. and Gerstein, H. C. 2000. Stress Hyperglycaemia and Increased Risk of Death after Myocardial Infarction in Patients with and without Diabetes: A Systematic Overview. *Lancet.* 355(9206): 773-778

Christensen, D. (2001). "Critical Care: Sugar Limit Saves Lives, *Science News.* Vol. 159. 159.

Coursin, D. B. and Murray, M. J. 2003. How Sweet Is Euglycemia in Critically Ill Patients? *Mayo Clin Proc.* 78(12): 1460-1462

Esposito, K., Marfella, R. and Giugliano, D. 2003. Stress Hyperglycemia, Inflammation, and Cardiovascular Events. *Diabetes Care.* 26(5): 1650-1651

Evans, M., Hastings, N. and Peacock, B. (1993). *Statistical Distributions*: Wiley.

Finney, S. J., Zekveld, C., Elia, A. and Evans, T. W. 2003. Glucose Control and Mortality in Critically Ill Patients. *Jama.* 290(15): 2041-2047

Knaus, W. A., Draper, E. A., Wagner, D. P. and Zimmerman, J. E. 1985. Apache II: A Severity of Disease Classification System. *Crit Care Med.* 13(10): 818-829

Krinsley, J. S. 2003. Association between Hyperglycemia and Increased Hospital Mortality in a Heterogeneous Population of Critically Ill Patients. *Mayo Clin Proc.* 78(12): 1471-1478

McCowen, K. C., Malhotra, A. and Bistrian, B. R. 2001. Stress-Induced Hyperglycemia. *Crit Care Clin.* 17(1): 107-124

Mizock, B. A. 2001. Alterations in Fuel Metabolism in Critical Illness: Hyperglycaemia. *Best Pract Res Clin Endocrinol Metab.* 15(4): 533-551

Ousman, Y. 2002. Hyperglycemia in the Hospitalized Patient. *Clinical Diabetes.* 20(3): 147-148

Patino, J. F., de Pimiento, S. E., Vergara, A., Savino, P., Rodriguez, M. and Escallon, J. 1999. Hypocaloric Support in the Critically Ill. *World J Surg.* 23(6): 553-559

Peck, P. (2004). Intensive Glucose Management Reduces in-Hospital Mortality. Proc *SCCM 33rd Annual Congress* in Orlando, Florida. 20-25 February 2004.

Robinson, M. K. 2002. Intensive Insulin Therapy in Critically Ill Patients - Current Summaries. *JPEN J Parenter Enteral Nutr.* 26(5): 317-318

Umpierrez, G. E., Isaacs, S. D., Bazargan, N., You, X., Thaler, L. M. and Kitabchi, A. E. 2002. Hyperglycemia: An Independent Marker of in-Hospital Mortality in Patients with Undiagnosed Diabetes. *J Clin Endocrinol Metab.* 87(3): 978-982

Van den Berghe, G., Wouters, P., Weekers, F., Verwaest, C., Bruyninckx, F., Schetz, M., Vlasselaers, D., Ferdinande, P., Lauwers, P. and Bouillon, R. 2001. Intensive Insulin Therapy in the Critically Ill Patients. *N Engl J Med.* 345(19): 1359-1367

Van den Berghe, G., Wouters, P. J., Bouillon, R., Weekers, F., Verwaest, C., Schetz, M., Vlasselaers, D., Ferdinande, P. and Lauwers, P. 2003. Outcome Benefit of Intensive Insulin Therapy in the Critically Ill: Insulin Dose Versus Glycemic Control. *Crit Care Med.* 31(2): 359-366

Weissman, C. 1999. Nutrition in the Intensive Care Unit. *Crit Care.* 3(5): R67-75

# 3

# CONTROL MODELLING AND ALGORITHMS

## 3.1 INTRODUCTION

In 1921, a young surgeon, Frederick Banting, and his graduate student assistant Charles Best prepared pancreas extracts which lowered the blood glucose level in dogs. Within months, this new revelation meant that sickly children with diabetes were returned almost to normal health with the aid of two insulin injections a day (Joslin, 1985). In 1939, Himsworth and Kerr were the first to establish an approach to measure in vivo insulin sensitivity (Derouich and Boutayeb, 2002).

### *3.1.1 Theoretical Solutions Proposed*

The integration of insulin and technology has meant that diabetes management has advanced greatly throughout the last century. With the ability to reduce blood glucose levels using insulin injections combined with the ability to measure blood glucose, plasma insulin and insulin sensitivity levels, the next step was to use mathematical models to estimate the relationships between glucose disappearance, insulin and insulin sensitivity.

These models capture the basic kinetics of glucose and insulin, enabling the development of management and control algorithms.

The development of insulin infusion programs has typically advanced along one of two paths. Simultaneously, both open-loop and closed-loop controllers have been proposed and have evolved through the work of numerous researchers (e.g. (Fisher, 1991; Furler, et al., 1985; Kienitz and Yoneyama, 1993; Lam, et al., 2002; Skyler, et al., 1981; Trajanoski and Wach, 1998). Semi closed-loop controllers, a compromise between open and closed-loop controllers, have also found their path in development (e.g (Chisholm, et al., 1984). Open-loop control programs deliver a predetermined infusion of insulin and are the simplest of the control types. At the other end of the scale, closed-loop controllers require regular, frequent glucose measurement and aim to replicate the function of the beta cells and the pancreas in endogenously regulating blood glucose levels. Closed-loop controllers are often complex as a result. Semi closed-loop methods, based on discrete, non-continuous blood glucose measurements, are appealing because of their simplicity when compared to the closed-loop system and their accuracy when compared to the open-loop system.

A number of researchers in the field of both diabetes and/or control systems have examined the possibility of automating insulin infusion using models (e.g (Bergman, et al., 1985; Cobelli, et al., 1998; 1999; Doyle, et al., 1996; Fisher, 1991; Furler, et al., 1985; Kienitz and Yoneyama, 1993; Kraegen and Chisholm, 1984; Skyler, et al., 1981; Trajanoski and Wach, 1998). The models presented range in complexity from the minimal model (Bergman, et al., 1985) $1^{st}$ order system to a $19^{th}$ order system model of the glucose-

regulatory system (Parker, et al., 1996) and use optimal control regimes such as H-infinity control (Kienitz and Yoneyama, 1993) and various structural controllers (Berger and Rodbard, 1991; Parker and Doyle, 2001). The need for continuous data or patient specific parameters has restricted the use of these models to computer simulations rather than clinical trials. However, the common priority has always been reduction in the absolute glucose excursion from basal, and the slope of the glucose excursion curve is typically neglected.

The simple feedback control method simulated by Furler et al (1985), works on the sliding-scale approach adopted in many hospitals and by many diabetics and clinicians, where insulin is delivered based on discrete blood glucose measurements. Lately, there has been a great deal of opposition to sliding-scale methods (Kletter, 1998; Radack, 1997; Sawin, 1997). In Furler et al's (1985) protocol, a linear relationship between the insulin demanded by the algorithm and the blood glucose value is determined to provide between 0.5 and 2.5 U/hr over the blood glucose range of 2 to 12 mmol/L, and is held at these limiting infusion values outside this range. This approach physiologically improves the research completed a year earlier by Chisholm et al (1984) who used the linear relationship between 0.5 and 2.5 U/hr of insulin over a blood glucose range of 4 to 8 mmol/L.

Both Chisholm et al's (1984) and Furler et al's (1985) approaches are reviewed in Fisher (1991), with Furler et al's (1985) being found to be superior in the control of elevated blood glucose levels. Fisher (1991) proposes that if the 3-hourly blood glucose is greater than or equal to 6 mmol/L the patient be given a bolus insulin injection proportional to the blood

glucose level squared, followed by a constant infusion independent to the blood glucose level. If the blood glucose is less than 6 mmol/L an unvarying infusion linearly proportional to the blood glucose measurement is maintained. These control regimes are shown in Figure 3.1.

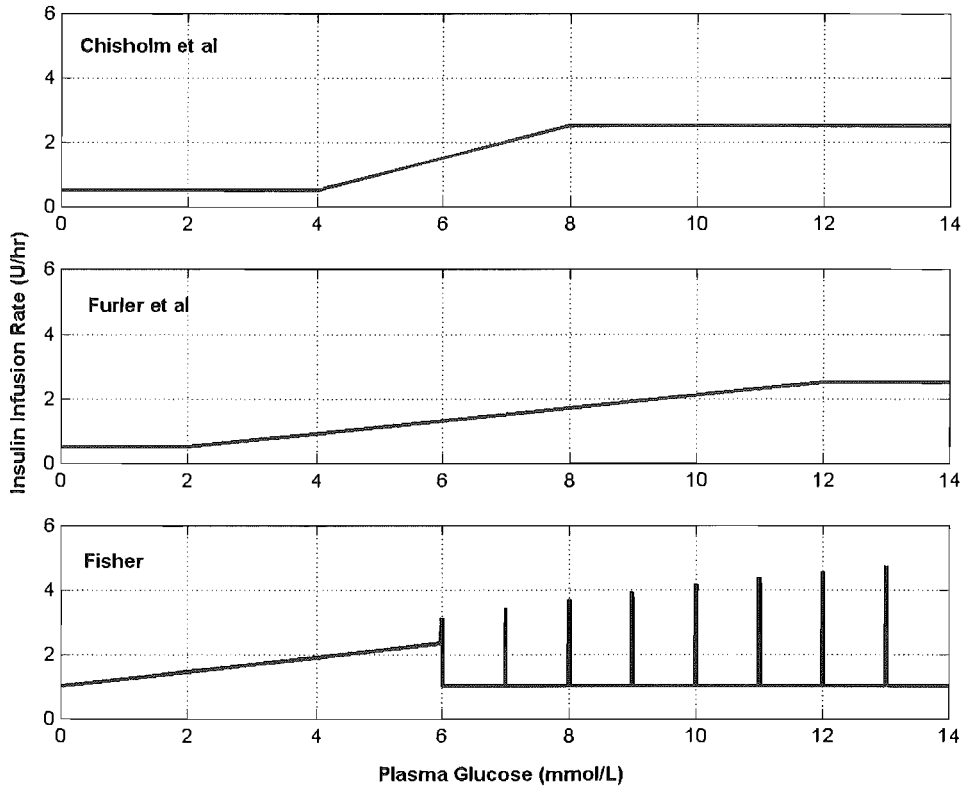


FIGURE 3.1: CONTROL REGIMES BY CHISHOLM ET AL (1984), FURLER ET AL (1985) AND FISHER (1991)

Both Fisher (1991) and Furler et al (1985) base their research on 3-hourly blood glucose measurements, but suggest that the stability of blood glucose control decreases as the sample interval is increased. This suggestion leads to the obvious enhancement of the equations by means of a smaller sample interval as proposed by Lam et al (Chase, et al., 2002; Lam, et al., 2002), and clinically trialled (Chase, et al., 2003; Doran, et al., 2004a; 2004b), where a 15 minute sample period is employed. This research, undertaken at the

University of Canterbury in conjunction with the Canterbury District Health Board, utilizes a heavy derivative control algorithm focusing on the slope of the glucose excursion curve as opposed to its absolute excursion from a target basal level, as shown in Figure 3.2. The advantage of focusing on the slope is that excursions can be minimized before they occur because the slope essentially predicts their occurrence. For example, a large positive slope on a blood glucose curve suggests the blood glucose will continue increasing and a larger insulin infusion rate is required. A small or negative slope suggests the blood glucose level is decreasing or changing direction, and hence only a small infusion or no infusion at all is required.

This control approach leads to the same results suggested by Fisher (1991), where a bolus injection is followed by a smaller infusion. However, it is more advanced in it's determination of the smaller infusion by its use of a basic glucose-insulin regulatory system model to design the control gains. In addition, the optimal steady state control solution for this model results in a single bolus of the exact size and time required to hold glucose levels constant in the face of a glucose challenge (Chase, et al., 2002; Lam, et al., 2002). Finally, in contrast to proportional control approaches that focus on blood glucose magnitude, this approach does not add insulin when blood glucose is dropping (Chase, et al., 2002; Lam, et al., 2002). As a result, it is potentially much safer with respect to hypoglycemic episodes.

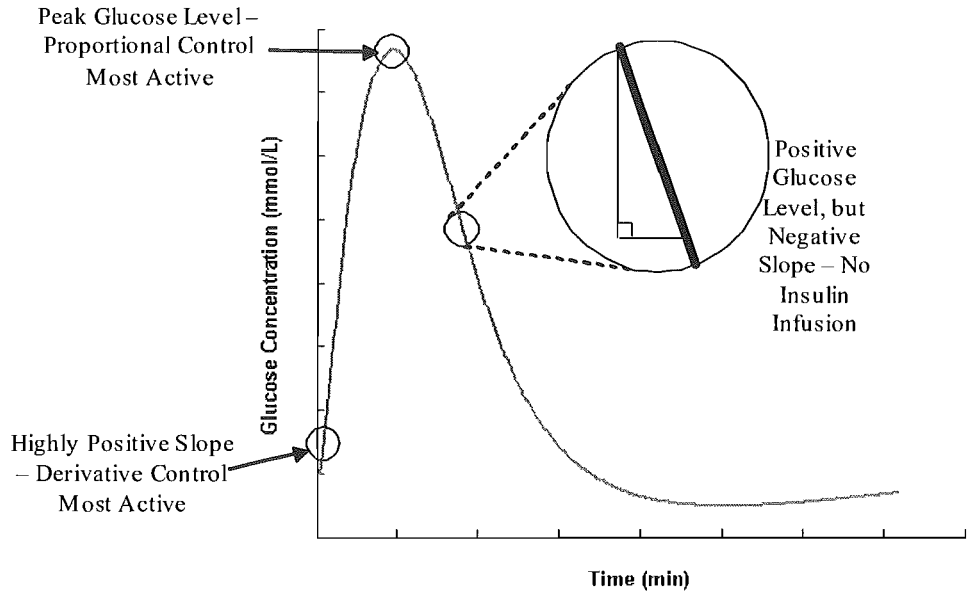


FIGURE 3.2: OGTT GLUCOSE PROFILE SHOWING CONTROL RESPONSE BASED ON SLOPE

### *3.1.2 First Mathematical Model*

Bolie (1961) was first to propose a mathematical model encompassing the effects of insulin on blood glucose levels. The simple model consisted of 2 equations and 5 patient parameters and assumed that the glucose disappearance was linearly related to both glucose and insulin levels. The insulin secretion is proportional to the glucose and the insulin disappears in proportion to the plasma insulin concentration. Bolie's (1961) model was the basis for following work by Akerman et al (1965), Corte et al (1970), and Segre et al (1973).

### *3.1.3 Bergman's 3 Compartment Minimal Model and Successors*

The 3 compartment minimal model developed by Bergman et al (1985) is the basic system for much of the further research in the use of controllers for diabetes management (e.g (Avogaro, et al., 1989; Bergman, et al., 1987; Caumo, et al., 1999; Cobelli, et al., 1998;

1999; De Gaetano and Arino, 2000; Pillonetto, et al., 2002; Vicini, et al., 1997; 1999). It is also the basis for many more advanced models with greater complexity (e.g. (Caumo, et al., 1999; Cobelli, et al., 1998; Hovorka, et al., 1998a) This model is comprised of 3 equations, modelling the exogenous glucose and it's interaction with insulin, insulin storage in a remote compartment, and insulin infusion and beta cell insulin production. Note that Bergman et al's (1985) original intent was to create a model to aid in the steady state determination of insulin sensitivity. However, it's simple kinetics capture the fundamental dynamics of the system relatively well and it is therefore ideal for control system design.

The use of a semi-closed loop algorithm for the control of blood glucose levels in diabetics was proposed and analysed in conjunction with the minimal model. (Fisher, 1991; Furler, et al., 1985) The analysis of the semi-closed loop algorithm by Fisher was verified by years of clinical experience when it predicted the best response to a meal input, was an insulin bolus followed by a continuous insulin infusion shown in Figure 3.1. Furler et al (1985) analysed a semi-closed loop system with an increased number of equations to include the effect of insulin-antibodies and removed the endogenous insulin secretion by the pancreas. Alternative patient specific parameter sets were also suggested and methods, by which the patient specific parameters could be found, using steady state analysis, were proposed.

The minimal model first proposed by Bergman et al (1985) forms the basis for the research undertaken. This model is physiologically verified and utilizes the concept of a remote compartment for insulin storage to account for the delay between insulin injection and utilization. The minimal model was designed to model metabolic physiology and simulate

basic glucose dynamics in vivo, and to be sufficiently simple enough that the patient specific parameters can be estimated using data from a frequently-sampled intravenous glucose tolerance test (FSIGTT). The minimal model is defined:

$$\dot{G} = -p_1 G - X(G + G_B) + P(t) \tag{3.1}$$

$$\dot{X} = -p_2 X + p_3 I \tag{3.2}$$

$$\dot{I} = -n(I + I_B) + u(t)/V_I \tag{3.3}$$

where :

$G$ = concentration of the plasma glucose above the basal level (mmol/L)

$G_B$ = basal level for plasma glucose concentration (mmol/L)

$X$ = normalised insulin in the remote compartment ($min^{-1}$)

$I$ = concentration of the plasma insulin above basal level (mU/L)

$I_B$ = basal level for plasma insulin concentration (mU/L)

$P(t)$ = exogenous glucose infusion rate (mmol/(L·min))

$u(t)$ = insulin infusion rate (mU /min)

$p_3$ = steady state insulin sensitivity parameter (L/ ($mU \cdot min^2$))

$V_I$ = assumed insulin distribution volume (L)

$p_1$ = fractional clearance of glucose at basal insulin ($min^{-1}$)

$p_2$ = delay in insulin action ($min^{-1}$)

$n$ = delay in subcutaneous transfer of insulin ($min^{-1}$)

Equations (3.1) and (3.2) describe the time course of plasma glucose concentration. The first equation encompasses glucose uptake dynamics dependent on the insulin concentration in the system and the introduction of exogenous glucose. The second equation expresses the insulin concentration dynamics of the remote compartment, and illustrates the time delay of distribution in the system. Equation (3.3) describes the time course of plasma insulin concentration and encompasses dynamics essential for defining insulin secretion by the β-cells in response to a glucose stimulus. Equations (3.1) and (3.2) – (3.3) were developed separately Insulin concentration is the outcome from the exogenous insulin infusion, $u(t)$, in Equations (3.2) and (3.3), and glucose input, $P(t)$, is the forcing function in Equation (3.1).

## 3.2 INTRAVENOUS MODEL DEVELOPMENT

### *3.2.1 Reduction to Two Compartments*

Implementing tight glucose control in critically ill patients via a fully automated insulin infusion system requires a simple model of the glucose regulatory system that accounts for the relationship between IV infusion of exogenous insulin and the measured blood glucose level. Bergman's three-compartment model, as shown in Equations (3.1) – (3.3), utilises the concept of a remote compartment (likened to the subcutaneous layer) for the storage of insulin to account for the subcutaneous transportation delay between the subcutaneous infusion of insulin and its utilization to reduce blood glucose levels.

Direct arterial/venous lines are typically available in critically ill patients for IV insulin infusion so that the system can be modelled using only two compartments. The first

compartment models insulin infusion and uptake into the blood, and the second models the blood glucose level and insulin mediated transport of glucose from the blood, as shown in Equations (3.4) and (3.5).

$$\dot{G} = -p_G G - S_I I(G + G_B) + P(t) \tag{3.4}$$

$$\dot{I} = -n(I + I_B) + {}^{u(t)}\!/_{V_I} \tag{3.5}$$

where:

$n$ = delay in interstitial transfer of insulin ($min^{-1}$)

$p_G$ = fractional clearance of plasma glucose at basal insulin ($min^{-1}$)

$S_I$ = insulin sensitivity (L/mU/min)

The two-compartment model removes the remote compartment, $X$, as defined by Equation (3.2), and combines the delay in insulin action, $p_2$, and the steady state insulin sensitivity parameter, $p_3$, into the insulin sensitivity ratio, $S_I = p_3/p_2$. In this case, the inclusions of a single parameter, SI, helps reduce underestimation of insulin sensitivity (McDonald, et al., 2000). Note that this very simple system still captures the fundamental dynamics of blood glucose rise and fall. However, its first order dynamics definition means that subtler, faster behaviours may be neglected. Figure 3.3 presents a mathematical schematic of both the two- and three- compartment models, including closed-loop feedback control blocks.

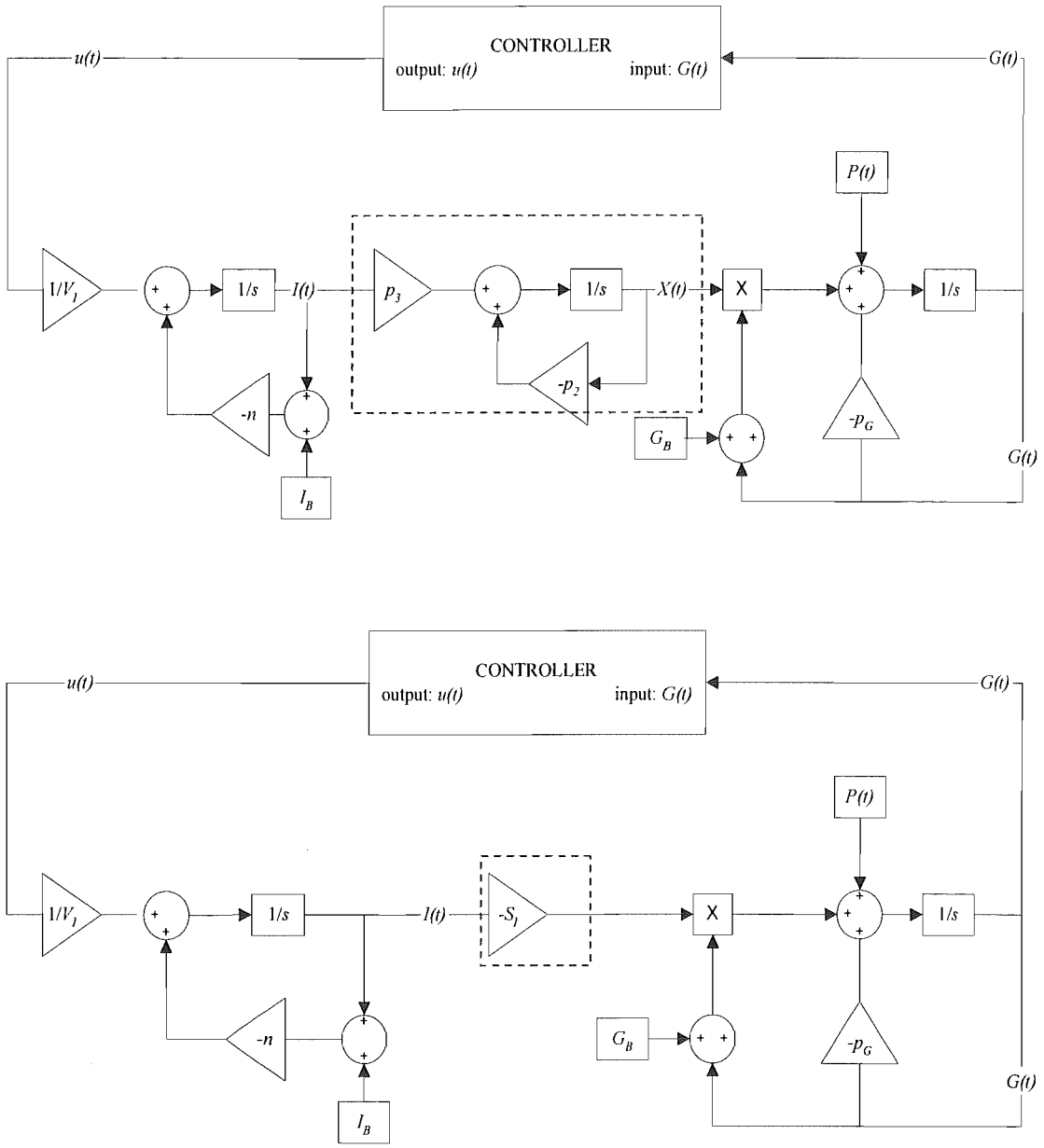


FIGURE 3.3: MATHEMATICAL SCHEMATIC OF BERGMAN'S 3-COMPARTMENT MODEL (TOP) AND THE REDUCED 2-COMPARTMENT MODEL (BOTTOM), BOTH INCLUDING FEEDBACK CONTROL

*Steady State Analysis Comparison*

An analysis was performed to show the equivalence of the two- and three- compartment models in the steady state. This analysis is presented in detail in Table 3.1, where a steady state value is denoted by the subscript '*ss*'. In contrast, the steady state values that result from testing certain inputs in step 'ix' are denoted by the subscript '∞'. The analysis shows that in the steady state, the models yield equivalent results for steady state plasma glucose, $G_{ss}$, and steady state insulin, $I_{ss}$, when $p_I \neq 0$.

Furthermore, both models result in $G_\infty = 0$ in the absence of exogenous glucose input when $p_1 = p_G \neq 0$. This result indicates that someone with measurable endogenous glucose removal (non-Type 1 diabetic individuals) will eventually reach basal level without external input. Similarly, if the individual is a Type 1 diabetic individual ($p_1 = p_G = 0$), then $G_\infty = \infty$ if there is any exogenous glucose input, as might be expected and $G_\infty = 0$ if there is not. These results show the models are equivalent and, in the steady state, capture the basic dynamic trends of the glucose-insulin regulatory system.

TABLE 3.1: STEADY STATE ANALYSIS FOR TWO- AND THREE-COMPARTMENT MODELS

| | | Three-Compartment Model | Two-Compartment Model |
|---|---|---|---|
| i. | Plasma Glucose Uptake Dynamics | $\dot{G} = -p_1 G - X(G + G_B) + P(t)$ | $\dot{G} = -p_G G - S_I I(G + G_B) + P(t)$ |
| ii. | Remote Compartment Insulin Dynamics | $\dot{X} = -p_2 X + p_3 I$ | N/A |
| iii. | Plasma Insulin Dynamics | $\dot{I} = -n(I + I_B) + u(t)/V_I$ | $\dot{I} = -n(I + I_B) + u(t)/V_I$ |
| iv. | Steady State | $\dot{G} = \dot{X} = \dot{I} = 0$<br>$P(t) = P_{ss}$<br>$u(t) = u_{ss}$ | $\dot{G} = \dot{I} = 0$<br>$P(t) = P_{ss}$<br>$u(t) = u_{ss}$ |
| v. | Steady State Plasma Insulin (from iii.) | $I_{ss} = I_B + u_{ss}/nV_I$ | $I_{ss} = I_B + u_{ss}/nV_I$ |
| vi. | Steady State Remote Compartment Insulin (from ii. and v.) | $X_{ss} = p_3/p_2 \, I_{ss} = S_I I_{ss}$<br>$X_{ss} = -S_I I_B + S_I u_{ss}/nV_I$ | N/A |
| vii. | Steady State Plasma Glucose (from i. and vi.) | $G_{ss} = \dfrac{-X_{ss} G_B + P_{ss}}{p_1 + X_{ss}}$ | $G_{ss} = \dfrac{-S_I I_{ss} G_B + P_{ss}}{p_G + S_I I_{ss}}$<br>$G_{ss} = \dfrac{-X_{ss} G_B + P_{ss}}{p_G + X_{ss}}$ |
| viii | Assume no prandial input, hence no exogenous insulin required | $P_{ss} = P(t = \infty) = 0$<br>$u_{ss} = u(t = \infty) = U_0 = nV_I I_B$ | $P_{ss} = P(t = \infty) = 0$<br>$u_{ss} = u(t = \infty) = U_0 = nV_I I_B$ |
| ix. | From assumptions in viii. | $I_\infty = -I_B + nV_I I_B/nV_I = 0$<br>$X_\infty = 0$<br>$G_\infty = 0 \quad if (p_1 \neq 0)$ | $I_\infty = -I_B + nV_I I_B/nV_I = 0$<br>$G_\infty = 0 \quad if (p_G \neq 0)$ |

### *3.2.2 Addition of Plasma Insulin Decay Dynamics*

During trials undertaken in 2002, utilising a heavy-derivative controller to control the rise of blood glucose following a glucose challenge of 75 g, it was found that Equations (3.4) – (3.5) lacked some form of accumulation dynamics (Chase, et al., 2003; Doran, et al., 2004a; 2004b). The initial two-compartment equations are linked solely by the insulin sensitivity constant, $S_I$, and hence at a given point in time it is assumed that the insulin in this compartment, $I(t)$, from previous time points is completely utilised and has no current effect. However, while it works in steady state analysis, this assumption is not accurate in transient dynamics. More specifically, the 2002 trials showed a so-called 'insulin accumulation dynamic', where the glucose level continued falling up to 180 minutes after a large insulin bolus-like infusion was given, clearly illustrating transient dynamics were missing from a model that could not capture this late drop.

The assumption made in the formulation of Bergman's three-compartment equations and hence the two-compartment model is therefore inherently flawed for transient dynamic cases. An addition to the model was required that accounted for un-utilised insulin in the plasma (Guyton and Hall, 1996) or that had bound then unbound to cell walls, tissues or insulin receptors (Duckworth and Kitabchi, 1981). This addition would have a similar effect to splitting the insulin compartment into a slow path and a fast path, which indicates the existence of fast and slow absorption channels and the presence of local insulin degradation (Cobelli, et al., 1999; Turnheim and Waldhausl, 1988; Wilinska, et al., 2003).

Turnheim and Waldhausl (1988) studied the pharmacokinetic modelling of intravenous insulin injection, and concluded that the concentration of plasma insulin following a bolus injection declines with at least two exponentials or two different rates. The first is a rapidly disappearing component of insulin represents elimination from the intravascular space, and the second is a more slowly disappearing component that reflects elimination from the interstitial fluid and the tissues that utilise insulin. These two components have half-lives of 2.4 and 50 – 130 minutes, respectively.

It should be noted that although insulin kinetics appear to be unchanged in diabetes mellitus patients, insulin removal may be retarded for cases with insulin antibodies or insulin resistance. ICU patients are likely to be in one of these two categories, hence changing the half-life values. The two exponentials can be approximated by one exponential relatively accurately for the time period up to 30 minutes after an insulin bolus, as shown in Figure 3.4, and hence for continuous infusions or for closely spaced bolus's, one exponential is sufficient in the model being developed, without significantly compromising physiological accuracy for minimised complexity.

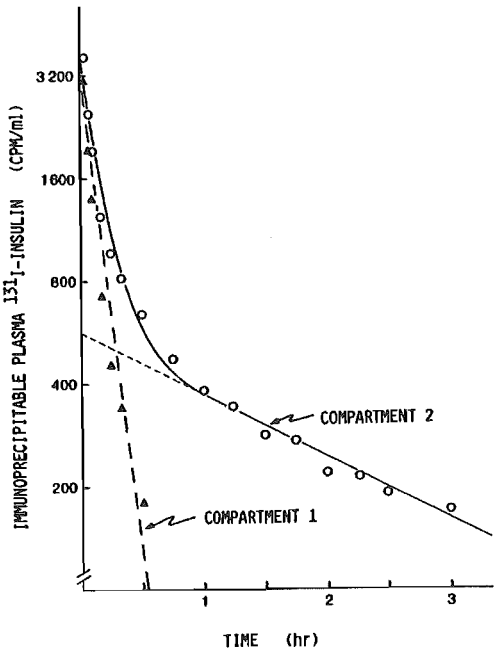


FIGURE 3.4: SEMI-LOGARITHMIC GRAPH OF INSULIN CONCENTRATION MODELLED BY 2 COMPARTMENTS (TURNHEIM AND WALDHAUSL, 1988)

Therefore, to account for the transient kinetics and utilisation of insulin, the plasma insulin concentration, $I$, in Equation (3.4) is replaced with a convolution integral to capture this effect, while Equation (3.5) is unchanged.

$$\dot{G} = -p_G G - S_I (G + G_B) k \int_0^t I(\tau) e^{-k(t-\tau)} d\tau + P(t) \tag{3.6}$$

where:

$k$ = Parameter controlling the effective half life of insulin ($min^{-1}$)

The convolution integral basically states that the removal of glucose as a result of the presence of insulin is a function of the currently available insulin, $I(t)$, as well as the remaining un-utilised insulin.

### *3.2.3 Available (Accessible) and Unavailable (Inaccessible) Glucose Compartments*

The model consisting of Equations (3.5) and (3.6) considers only available glucose, as the available glucose directly measured effects the plasma glucose levels, whereas the effects from unavailable glucose are less measurable. Work by Vicini et al (1997; 1999) and Caumo et al (1999) considers only labelled tracer glucose (called hot glucose) and is split into an accessible pool (denoted by the subscript 1) and a slowly equilibrilating pool (denoted by the subscript 2), as shown in Figure 3.5. The accessible pool is where insulin independent glucose disposal takes place and includes tissues in rapid equilibrium with plasma such as the red blood cells, central nervous system, kidneys and liver. The second, slowly equilibrilating pool includes insulin dependent tissues such as muscle and fat. The split of glucose between the two pools is 60:40 (Caumo, et al., 1999). Guyton and Hall (1996) state that "ordinarily, only about 60 per cent of the glucose in the meal is stored ... in the liver and then returned later" which lines up with the 60:40 split made by Caumo, but may only be accurate in the zero input, steady state condition.

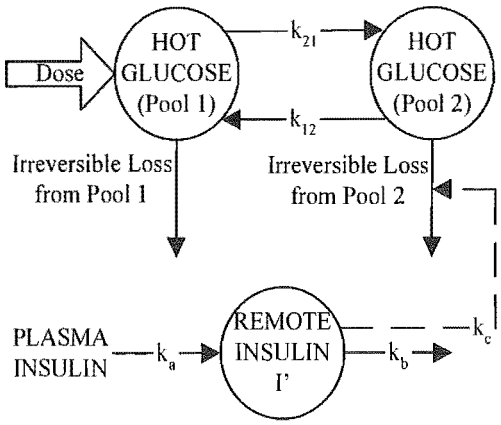


FIGURE 3.5: TWO COMPARTMENT GLUCOSE MODEL (CAUMO, ET AL., 1999; VICINI, ET AL., 1997, 1999)

This model is based on the minimal model, and hence is not too dissimilar to the current model presented. In the current model, the effect of glucose removal via the kidney, liver and central nervous system is lumped into the glucose clearance parameter, $p_G$, and hence the system model considers the glucose to be all in the accessible compartment, a so-called 'cold' model (Caumo, et al., 1999). In addition, when the literature discusses the minimal model underestimating insulin sensitivity (Caumo, et al., 1999; Cobelli, et al., 1998; 1999; Vicini, et al., 1997, 1999) the result should be expected, as the glucose is modelled as all accessible, and hence bigger than in Caumo et al's (1999) work. As the product of the insulin sensitivity, $S_I$, a glucose term, $(G+G_B)$, and an insulin term, $I$, are considered together in the model, if the glucose term, $G$, is increased, it follows that insulin sensitivity, $S_I$, will be decreased. However, other reasons for this underestimation might include insulin saturation at large doses as the works described (Caumo, et al., 1999; Cobelli, et al., 1998; 1999; Vicini, et al., 1997; 1999) utilise clamp tests with high insulin doses. When the insulin doses given are lower, the result is an increased insulin sensitivity value, $S_I$ (Prigeon, et al., 1996). More specifically, splitting into two glucose compartments based on a steady state glucose disposal ratio may not be the most physiologically justified modelling choice in capturing transient behaviours.

### *3.2.4 Omission of Endogenous Insulin Production*

It is unsure to what extent a hyperglycemic critically ill patient's endogenous insulin production is impaired or what its exact dynamics are. As the reasons for stress-induced hyperglycemia in ICU patients vary widely, so also do their primary metabolic responses. In particular, stress hormones such as adrenaline and cortisol inhibit endogenous insulin production (Mizock, 2001). As a result of their condition and treatment, it has always been difficult to quantify a value for endogenous insulin production and plasma insulin basal level during trials to date (Doran, et al., 2004a; 2004b). In Bergman's three-compartment model and the reduced two-compartment model, both exogenous insulin infusion, $u(t)$, and endogenous insulin production, $I(t)$, are included. Control regimes developed for this and related research include an endogenous insulin production value, $U_0$, which has generally been set to be equivalent to 1-2 U/hr, and a basal insulin concentration, $I_B$ set to 15 mU/L (Chase, et al., 2003; Doran, et al., 2004a; 2004b; Lam, et al., 2002).

Initially, due to the difficultly in directly measuring these parameters, the assumed values for endogenous insulin production, $U_0$, and basal insulin concentration, $I_B$, were removed from the model to minimise the unknowns and potential variability. In addition, it can be assumed that ICU patients with steady feeds and hyperglycemia are in a moderately steady condition with relevantly constant endogenous insulin production. Therefore, the basal insulin production can be assumed to be a 'static' offset and its effect lumped into the endogenous fractional glucose removal parameter, $p_G$. Additionally, the insulin sensitivity parameter, $S_I$, is a relative value that already encompasses a number of physiological phenomena such as receptor sensitivity, losses in the bloodstream and effects of external

perturbations such as drug therapies, so this approach minimises complexity by keeping only two, now potentially time varying, parameters, $p_G$ and $S_I$, to govern glucose removal. Equation (3.7) defines the new rate of change of plasma insulin concentration.

$$\dot{I} = -nI + \frac{u(t)}{V_I} \tag{3.7}$$

However, in the case of no exogenous insulin input, endogenous insulin secretion is not suppressed. The model was modified to include the effect of basal endogenous insulin, which is required for periods of no exogenous insulin infusion, as when $u(t) = 0$.

$$\dot{I} = -nI + \frac{u(t)}{V_I} + \frac{e^{(-u(t))} I_B}{V_I} \tag{3.8}$$

The endogenous insulin production is equal to the basal insulin value dispersed through the insulin distribution volume, $\frac{I_B}{V_I}$ for these periods. As the exogenous insulin infusion, $u(t)$, is increased, endogenous insulin, $I_B$, is suppressed, so hence large values of exogenous insulin infusions, $u(t)$, Equation (3.8) becomes:

$$\dot{I} \approx -nI + \frac{u(t)}{V} \tag{3.9}$$

However, unpublished trials using Equations (3.6) and (3.7) still did not accurately capture all transient dynamics. In addition, good data fits required extensive variation of patient specific parameters, $p_G$ and $S_I$, (50 - 100%) over short, unrealistic periods of time (1 - 2

hours). Hence, additional insulin dynamics are still missing. In particular, dynamics that capture the reduced glucose decrement resulting from large insulin boluses or infusions are required to account for saturation effects.

### *3.2.5 Insulin Saturation*

The concentration of insulin in the blood is a function of several variables. Once insulin has entered the human circulatory system, its distribution is likely to be uneven because of differences in blood perfusion, tissue binding, and permeability of cell membranes (Guyton and Hall, 1996). To add to this complexity, the insulin concentration at any time is dependent on its appearance in the circulation, binding to plasma proteins, distribution in, and exchange among, body pools, and irreversible disappearance from the circulation (Del Prato, et al., 2002; Mari, et al., 2001; Thorsteinsson, 1990).

When insulin enters the human circulatory system, it initiates its effects on target cells by first binding, then activating a membrane receptor protein. It is the activated receptor, not the insulin, that causes the subsequent effects. Increased permeability to glucose is a result of insulin binding to receptor cells, and the effects of this binding are that approximately 80% of the cells in the body become highly permeable to glucose and the rate of transport of glucose into the resting muscle cell is increased by a factor of at least 15 (Guyton and Hall, 1996).

During the 1970's and 1980's a string of papers were published regarding the plasma insulin disappearance kinetics in humans. Many found flaws in the first order (linear)

assumptions of insulin disappearance that had been predominantly used in previous models (e.g. (Insel, et al., 1974; McGuire, et al., 1979; Sherwin, et al., 1974; Toffolo, et al., 1980). These flaws were assumed to be based on the narrow range of insulin levels studies, with the first results of a study which showed non-proportionality between plasma concentration and plasma disappearance rate first reported by Sönksen et al (1973). Hence, experimental studies were undertaken to determine whether the insulin disappearance rate was proportional to the plasma insulin concentration, by considering the concentrations resulting from a series of intravenous insulin infusions at different rates in both normal and diabetic subjects.

The proposed models generally employed Michaelis-Menten saturation mechanisms. Michaelis-Menten kinetics are assumed for a variety of biological phenomenon, and stem from a set of assumptions about what may be occurring at the molecular level on a cell's surface (Edelstein-Keshet, 1988; Joslin, 1985). The saturation mechanism demonstrates that even though insulin in the system may be highly abundant, the number of insulin receptors determines the number of binding sites and hence the extent and rate of insulin action. Saturation via Michaelis-Menten kinetics is generally modelled:

$$K(C) = \frac{K_{\max} C}{K_n + C} \tag{3.10}$$

where :

$K(C)$ = insulin action as a function of concentration

$K_{\max}$ = maximal insulin disappearance rate via a saturable pathway

$K_n$ = plasma insulin concentration where insulin disappearance is half maximal

$C$ = plasma insulin concentration

Fugleberg et al (1982) investigated a kinetic model of insulin disappearance in which insulin was assumed to be extracted from the plasma by two independent processes, one saturable and one non-saturable. This assumption was consistent with Franckson and Ooms' (1973; 1973) findings in normoglycemic dogs, and Sönksen et al's (1973) findings in normoglycemic humans. However, interpretation of Sönksen et al's (1973) findings showed that severe hypoglycemia had occurred during their experiment, so it is difficult to use these results as validation. Fugleberg et al (1982) concluded that the plasma insulin disappearance could be described by the proposed kinetic model, and likened the saturable pathway to hepatic insulin degradation, and the non-saturable pathway to renal clearance.

Thorsteinsson (1990) reviewed three kinetic models including the saturable and non-saturable pathway model. The three potential models are shown in Figure 3.6. The first model, identical to the one proposed by Fugleberg et al in 1986, considers the case where both saturable and non-saturable (linear) mechanisms exist, and is defined in Equation (3.11). The second model represents just the saturation kinetics by means of the Michaelis-Menten saturation model, and is defined in Equation (3.12). The third model represents first order (linear, non-saturable) appearance of insulin, and is defined in Equation (3.13).

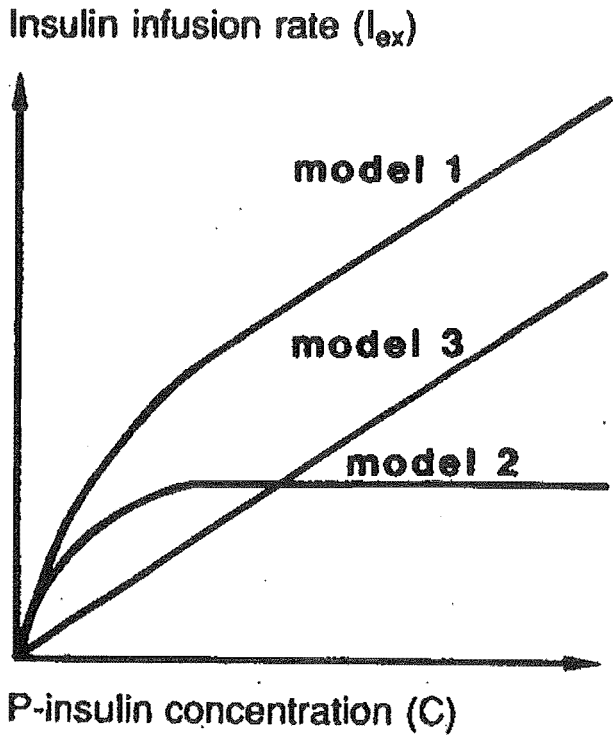


FIGURE 3.6: KINETIC MODELS FOR INSULIN AVAILABILITY (THORSTEINSSON, 1990)

$$I_{ex} = -I_{end} + k_1 C + \frac{k_2 C}{k_3 + C} \tag{3.11}$$

$$I_{ex} = -I_{end} + \frac{k_2 C}{k_3 + C} \tag{3.12}$$

$$I_{ex} = -I_{end} + k_1 C \tag{3.13}$$

where :

$I_{ex}$ = exogenous infusion rate (pmol/kg/min)

$I_{end}$ = endogenous infusion rate (pmol/kg/min)

$C$ = steady state plasma insulin concentration (pmol/L)

$k_1$ = insulin clearance rate via a non-saturable pathway (L/min)

$k_2$ = maximal insulin disappearance rate via a saturable pathway (nmol/min)

$k_3$ = plasma insulin concentration at which the insulin disappearance rate via a saturable mechanism is half maximal (nmol/L)

Thorsteinsson (1990) concluded that the second model, using saturation kinetics alone, was superior to the other models for normal subjects at physiological and supraphysiological plasma insulin concentrations, and for diabetics at supraphysiological conditions. The appropriate model at physiological insulin concentrations for type 1 diabetic patients was that of first order kinetics alone, the third model.

Generally, insulin appearance calculated using Michaelis-Menten kinetics were larger than those calculated using first order kinetics, and it is hypothesised that first order kinetics underestimates clearance rates by 20-30%. The effects of physiological and pathological conditions were considered using the saturation kinetics model. The effect of age, sex and relative body weight, within 80-130% of the ideal body weight, was minimal on insulin appearance. Insulin appearance has been found to be related to the relative muscle mass and inversely related to the size of adipose (fat) tissue in young healthy subjects of normal weight. In severely obese individuals, greater than twice the ideal body weight, the insulin appearance was normal or reduced. In addition, high levels of insulin antibodies can also increase the insulin clearance rate because infused insulin is rapidly bound to antibodies, resulting in a lower steady state plasma free insulin concentration and hence a greater metabolic clearance rate (Thorsteinsson, 1990).

Hence, the evidence is significantly in favour of adding insulin saturation to the model presented. As the saturation is on the appearance of insulin, the Michaelis-Menten saturation dynamics were added to the plasma insulin concentration compartment. The result is another revision to Equation (3.5).

$$\dot{I} = -\frac{nI}{1+\alpha_I I} + {}^{u(t)}\!/\!_{V_I} \tag{3.14}$$

where :

$\alpha_I$ = Michaelis-Menten parameter for saturation

Previously, insulin saturation effects were not included in the model and saturation effects were seen as reduced insulin sensitivity, $S_I$. By including insulin saturation, variations in the insulin sensitivity, $S_I$, should be reduced and more physiologically realistic. Hence, the cyclical and drug-induced effects on insulin sensitivity should be more clearly visible.

### *3.2.6 Glucose Clearance Saturation*

Glucose clearance due to exogenous insulin is controlled primarily by the insulin sensitivity parameter, $S_I$, which links exogenous insulin and endogenous glucose levels. To improve model accuracy, the incorporation of the glucose response to varying doses was investigated. As the dose of exogenous insulin is increased insulin sensitivity, $S_I$, decreases (Prigeon, et al., 1996). This result occurs because the effect of insulin saturation at the receptor, limiting utilisation (Natali, et al., 2000). Hence, there is a need for a saturable mechanism in the model to account for this non-linear effect. Prigeon et al (1996)

concluded that as results were not consistent with the known saturation characteristics of insulin action on tissue, a second saturable site involving the transport of insulin from plasma to interstitium might also be a possibility.

Using a Michaelis-Menten function of insulin concentration with a delay of $t_{1/2}$, Natali et al (2000) added a saturation to insulin action on fractional glucose extraction in the circulatory model shown in Figure 3.7. Natali et al (2000) was able to obtain good fits to 7 lean and obese patients, with limitations only occurring in the first 60 minutes, which was attributed to an irregular onset of insulin action during this initial phase. The glucose clearance for this research was defined:

$$Cl \propto \left[ E_b + \frac{E_{\max}(I - I_B)}{EC_{50} + (I - I_B)} \right] \tag{3.15}$$

where :

$Cl$ = Glucose clearance (mL/min/m$^2$)

$E_b$ =basal glucose fractional extraction

$E_{\max}$ = maximal glucose fractional extraction via a saturable mechanism

$EC_{50}$ = plasma insulin concentration at which the glucose fractional extraction rate via a saturable mechanism is half maximal

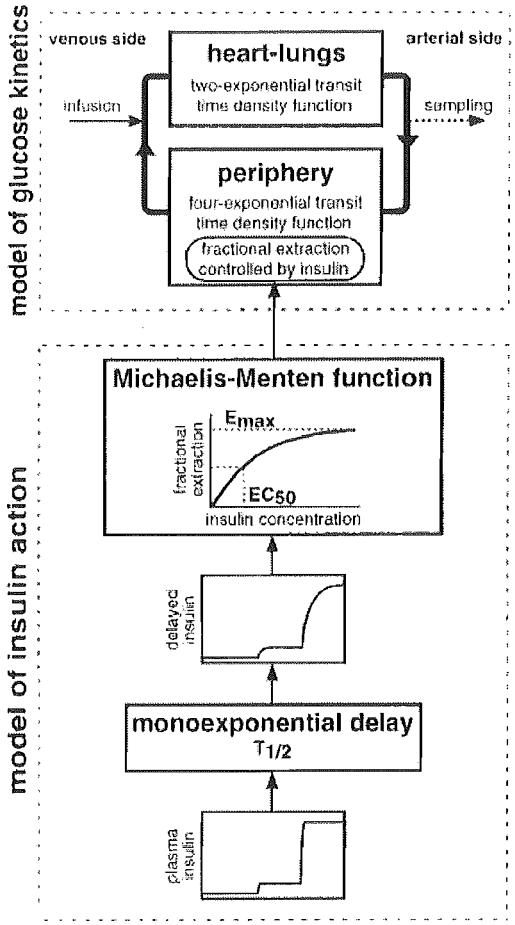


FIGURE 3.7: NATALI ET AL'S (2000) MODEL INCLUDING SATURATION OF GLUCOSE EXTRACTION

The addition of a saturation term for the effect of exogenous insulin changes Equation (3.6).

$$\dot{G} = -p_G G - S_I (G + G_B) \frac{Q}{1 + \alpha_G Q} + P(t) \tag{3.16}$$

$$Q = k \int_0^t I(\tau) e^{-k(t-\tau)} d\tau \tag{3.17}$$

where:

$\alpha_G$ = Michaelis-Menten glucose clearance rate saturation parameter

### 3.3 FINAL FORM OF MODEL

The model has been developed to account for non-linear saturation of exogenous insulin appearance rate and its saturable utilisation to reduce blood glucose levels. The reduction of the minimal model from three to two compartments accounts for IV infusion and is verified for the steady state. The addition of transient insulin kinetics via a convolution integral on exogenous plasma insulin concentration and its utilisation has accounted for the accumulation dynamic seen in prior clinical trials, and better matches physiological knowledge. This modelling approach also effectively splits the glucose compartment into fast and slow (or available and unavailable) compartments over a continuum rather than two discrete states (Caumo, et al., 1999; Cobelli, et al., 1999; Vicini, et al., 1997).

Removing endogenous insulin production from the model for periods of exogenous insulin infusions reduced model complexity and improved model parameter fits. The addition of insulin appearance and glucose clearance saturation are physiologically justified and added via Michaelis-Menten dynamics. The resulting non-linear model is now defined:

$$\dot{G} = -p_G G - S_I (G + G_B) \frac{Q}{1 + \alpha_G Q} + P(t) \tag{3.18}$$

$$Q = k \int_0^t I(\tau) e^{-k(t-\tau)} d\tau \tag{3.19}$$

$$\dot{I} = -\frac{nI}{1 + \alpha_I I} + \frac{u(t)}{V_I} + \frac{e^{(-u(t))} I_B}{V_I} \tag{3.20}$$

which is equivalent to the three compartment model defined

$$\dot{G} = -p_G G - S_I(G + G_B)\frac{Q}{1+\alpha_G Q} + P(t) \tag{3.21}$$

$$\dot{Q} = -kQ + kI \tag{3.22}$$

$$\dot{I} = -\frac{nI}{1+\alpha_I I} + \frac{u(t)}{V_I} + \frac{e^{(-u(t))}I_B}{V_I} \tag{3.23}$$

where $Q$ represents the effects of the insulin decay half-life in the plasma and is similar to the model found in Mari et al (2001). The final form of the non-linear model is shown in Figure 3.8.

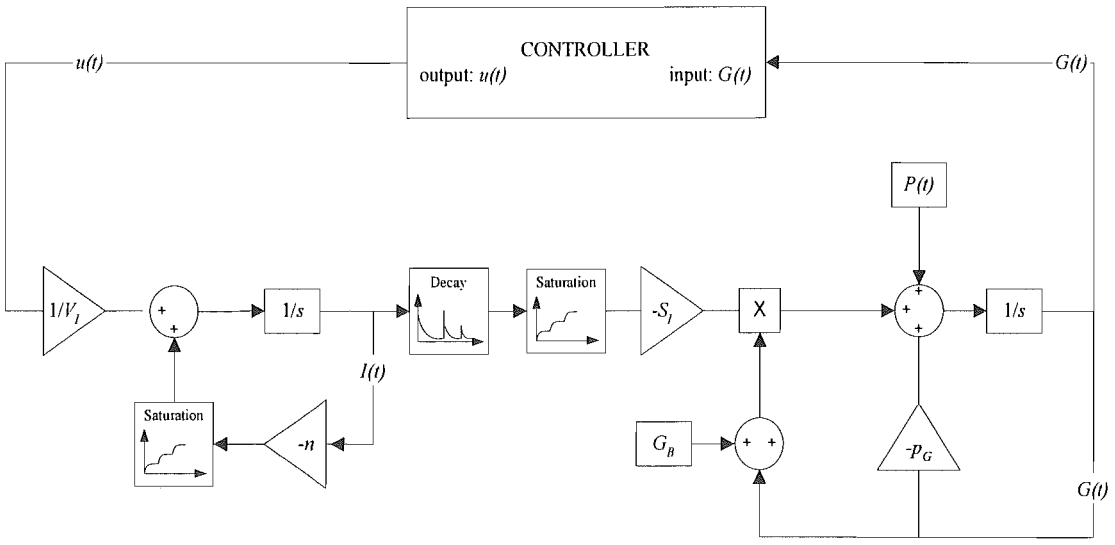


FIGURE 3.8: MATHEMATICAL SCHEMATIC OF THE FINAL FORM OF THE CONTROL MODEL INCLUDING FEEDBACK CONTROL

The model developed, shown by Equations (3.19) – (3.21) and in Figure 3.8, is similar in overall form to the initial two-compartment model, shown in Equations (3.4) – (3.5) and in Figure 3.3, but has a number of significant differences. The effect of exogenous insulin in the plasma in the time period following its infusion and the saturation of insulin appearance and glucose clearance have been added, while the endogenous insulin production, $U_0$, and basal level, $I_B$, have been lumped into the endogenous glucose parameter, $p_G$, removing two less well defined model parameters. In addition, non-linear saturation of insulin appearance and utilisation have been added, per results in the literature. Finally, the second compartment in Equation (3.21) has equal constants, $k$, preventing the undermodelling of insulin sensitivity, $S_I$ (Caumo, et al., 1999).

### *3.3.1 Steady State Analysis*

A steady state analysis was performed to show the equivalence of both of the two-compartment models in the steady state. This analysis is presented in detail in Table 3.2. It should be noted that in the assumption of no exogenous insulin, the steady state insulin infusion, $u_{ss}$, differs between the two models, as the final form assumes no endogenous insulin, $u_{ss} = 0$, and the two-compartment model assumes $u_{ss} = U_0$. However, both assumptions lead to the same steady state value as shown in steps (ix) and (xi).

TABLE 3.2: STEADY STATE ANALYSIS FOR NEW MODEL AND ORIGINAL TWO-COMPARTMENT MODEL

| | | Final Form of Model | Two-Compartment Model |
|---|---|---|---|
| i. | Plasma Glucose Uptake Dynamics | $\dot{G} = -p_G G - S_I(G+G_B)\frac{Q}{1+\alpha_G Q} + P(t)$ | $\dot{G} = -p_G G - S_I I(G+G_B) + P(t)$ |
| ii. | Plasma Insulin Decay | $\dot{Q} = -kQ + kI$ | N/A |
| iii. | Plasma Insulin Dynamics | $\dot{I} = -\frac{nI}{1+\alpha_I I} + \frac{u(t)}{V_I} + \frac{e^{(-n(t))}I_B}{V_I}$ | $\dot{I} = -n(I+I_B) + {u(t)}/{V_I}$ |
| iv. | Steady State | $\dot{G} = \dot{Q} = \dot{I} = 0$<br>$P(t) = P_{ss}$<br>$u(t) = u_{ss}$ | $\dot{G} = \dot{I} = 0$<br>$P(t) = P_{ss}$<br>$u(t) = u_{ss}$ |
| v. | Steady State Plasma Insulin (from iii.) | $I_{ss} = \frac{u_{ss}}{nV_I - \alpha_I u_{ss}}$ | $I_{ss} = I_B + {u_{ss}}/{nV_I}$ |
| vi. | Plasma Insulin Decay Steady State (from ii. and v.) | $Q_{ss} = I_{ss}$ | N/A |
| vii. | Steady State Plasma Glucose (from i. and vi.) | $G_{ss} = \frac{-S_I I_{ss} G_B + P_{ss} + \alpha_G I_{ss} P_{ss}}{p_G + S_I I_{ss} + \alpha_G I_{ss} p_G}$ | $G_{ss} = \frac{-S_I I_{ss} G_B + P_{ss}}{p_G + S_I I_{ss}}$ |
| viii | Assume no prandial input, and no exogenous insulin | $P_{ss} = P(t=\infty) = 0$<br>$u_{ss} = u(t=\infty) = 0$ | $P_{ss} = P(t=\infty) = 0$<br>$u_{ss} = u(t=\infty) = U_0 = nV_I I_B$ |
| ix. | From assumptions in viii. | $I_\infty = 0 \quad Q_\infty = 0$<br>$G_\infty = 0 \quad if\,(p_G \neq 0)$ | $I_\infty = -I_B + {nV_I I_B}/{nV_I} = 0$<br>$G_\infty = 0 \quad if\,(p_G \neq 0)$ |
| x. | Assume no exogenous insulin | $u_{ss} = u(t=\infty) = 0$ | $u_{ss} = u(t=\infty) = U_0 = nV_I I_B$ |
| xi. | From assumptions in x. | $I_\infty = 0 \quad Q_\infty = 0$<br>$G_\infty = {P_{ss}}/{p_G} \quad if\,(p_G \neq 0)$ | $I_\infty = 0$<br>$G_\infty = {P_{ss}}/{p_G} \quad if\,(p_G \neq 0)$ |

## 3.4 REFERENCES

Akerman, E., Gatewood, L., Rosevear, J. and Molnar, G. 1965. Model Studies of Blood Glucose Regulation. *Bull. Math. Biophys.* 27: 21-37

Avogaro, A., Bristow, J. D., Bier, D. M., Cobelli, C. and Toffolo, G. 1989. Stable-Label Intravenous Glucose Tolerance Test Minimal Model. *Diabetes.* 38(8): 1048-1055

Berger, M. P. and Rodbard, D. 1991. A Pharmacodynamic Approach to Optimizing Insulin Therapy. *Comput Methods Programs Biomed.* 34(4): 241-253

Bergman, R. N., Finegood, D. T. and Ader, M. 1985. Assessment of Insulin Sensitivity in Vivo. *Endocr Rev.* 6(1): 45-86

Bergman, R. N., Prager, R., Volund, A. and Olefsky, J. M. 1987. Equivalence of the Insulin Sensitivity Index in Man Derived by the Minimal Model Method and the Euglycemic Glucose Clamp. *J Clin Invest.* 79(3): 790-800

Bolie, V. W. 1961. Coefficients of Normal Blood Glucose Regulation. *J Appl Physiol.* 16: 783-788

Caumo, A., Vicini, P., Zachwieja, J. J., Avogaro, A., Yarasheski, K., Bier, D. M. and Cobelli, C. 1999. Undermodeling Affects Minimal Model Indexes: Insights from a Two-Compartment Model. *Am J Physiol.* 276(6 Pt 1): E1171-1193

Chase, J. G., Lam, Z. H., Lee, J. Y. and Hwang, K. S. (2002). Active Insulin Infusion Control of the Blood Glucose Derivative. Proc *Proc. of the 7th International Conf on Control, Automation, Robotics and Vision (ICARCV 2002)* in Singapore.

Chase, J. G., Shaw, G. M., Doran, C. V., Hudson, N. H. and Moorhead, K. T. (2003). Derivative Weighted Active Insulin Control Algorithms and Trials. Proc *IFAC Symposium* in Melbourne, Australia.

Chisholm, D. J., Kraegen, E. W., Bell, D. J. and Chipps, D. R. 1984. A Semi-Closed Loop Computer-Assisted Insulin Infusion System. Hospital Use for Control of Diabetes in Patients. *Med J Aust.* 141(12-13): 784-789

Cobelli, C., Bettini, F., Caumo, A. and Quon, M. J. 1998. Overestimation of Minimal Model Glucose Effectiveness in Presence of Insulin Response Is Due to Undermodeling. *Am J Physiol.* 275(6 Pt 1): E1031-1036

Cobelli, C., Caumo, A. and Omenetto, M. 1999. Minimal Model SG Overestimation and SI Underestimation: Improved Accuracy by a Bayesian Two-Compartment Model. *Am J Physiol.* 277(3 Pt 1): E481-488

Corte, M., Romano, S., Voeghelin, M. and Serio, M. 1970. On a Mathematical Model for the Analysis of the Glucose Tolerance Curve. *Diabetes.* 19: 445-449

De Gaetano, A. and Arino, O. 2000. Mathematical Modelling of the Intravenous Glucose Tolerance Test. *J Math Biol.* 40(2): 136-168

Del Prato, S., Marchetti, P. and Bonadonna, R. C. 2002. Phasic Insulin Release and Metabolic Regulation in Type 2 Diabetes. *Diabetes.* 51 Suppl 1: S109-116

Derouich, M. and Boutayeb, A. 2002. The Effect of Physical Exercise on the Dynamics of Glucose and Insulin. *J Biomech.* 35(7): 911-917

Doran, C. V., Chase, J. G., Shaw, G. M., Moorhead, K. T. and Hudson, N. H. 2004a. Automated Insulin Infusion Trials in the ICU. *Diabetes Technology and Therapeutics.* 6(2)

Doran, C. V., Moorhead, K. T., Hudson, N. H., Chase, J. G. and Shaw, G. M. 2004b. Derivative Weighted Active Insulin Control Modelling and Clinical Trials for ICU Patients. *Med Eng Phys.* -to appear

Doyle, F. J., 3rd, Dorski, C., Harting, J. E. and Peppas, N. A. (1996). Control and Modelling of Drug Delivery Devices for the Treatment of Diabetes. Proc *American Control Conference* in Seattle, Washington, USA.

Duckworth, W. C. and Kitabchi, A. E. 1981. Insulin Metabolism and Degradation. *Endocr Rev.* 2(2): 210-233

Edelstein-Keshet. (1988). *Mathematical Models in Biology.* New York: Random House.

Fisher, M. E. 1991. A Semiclosed-Loop Algorithm for the Control of Blood Glucose Levels in Diabetics. *IEEE Trans Biomed Eng.* 38(1): 57-61

Franckson, J. R. and Ooms, H. A. 1973. The Catabolism of Insulin in the Dog: Evidence for the Existence of Two Catabolic Pathways. *Postgrad Med J.* 49: Suppl 7:931-939

Franckson, J. R. and Ooms, H. A. 1973. The Glomerular Clearance of Exogenous Insulin. *Horm Metab Res.* 5(2): 75-79

Fugleberg, S., Kolendorf, K., Thorsteinsson, B., Bliddal, H., Lund, B. and Bojsen, F. 1982. The Relationship between Plasma Concentration and Plasma Disappearance Rate of Immunoreactive Insulin in Normal Subjects. *Diabetologia.* 22(6): 437-440

Furler, S. M., Kraegen, E. W., Smallwood, R. H. and Chisholm, D. J. 1985. Blood Glucose Control by Intermittent Loop Closure in the Basal Mode: Computer Simulation Studies with a Diabetic Model. *Diabetes Care.* 8(6): 553-561

Guyton, A. C. and Hall, J. E. (1996). Insulin, Glucagon, and Diabetes Mellitus, *Textbook of Medical Physiology.* 971-983: W.B. Saunders Company.

Hovorka, R., Chassin, L., Luzio, S. D., Playle, R. and Owens, D. R. 1998a. Pancreatic Beta-Cell Responsiveness During Meal Tolerance Test: Model Assessment in

Normal Subjects and Subjects with Newly Diagnosed Noninsulin-Dependent Diabetes Mellitus. *J Clin Endocrinol Metab.* 83(3): 744-750

Insel, P. A., Kramer, K. J., Sherwin, R. S., Liljenquist, J. E., Tobin, J. D., Andres, R. and Berman, M. 1974. Modeling the Insulin-Glucose System in Man. *Fed Proc.* 33(7): 1865-1868

Joslin, E. P. (1985). *Joslin's Diabetes Mellitus*: Lea & Febiger.

Kienitz, K. H. and Yoneyama, T. 1993. A Robust Controller for Insulin Pumps Based on H-Infinity Theory. *IEEE Trans Biomed Eng.* 40(11): 1133-1137

Kletter, G. G. 1998. Sliding Scale Fallacy. *Arch Intern Med.* 158(13): 1472

Kraegen, E. W. and Chisholm, D. J. 1984. Insulin Responses to Varying Profiles of Subcutaneous Insulin Infusion: Kinetic Modelling Studies. *Diabetologia.* 26(3): 208-213

Lam, Z. H., Hwang, K. S., Lee, J. Y., Chase, J. G. and Wake, G. C. 2002. Active Insulin Infusion Using Optimal and Derivative-Weighted Control. *Med Eng Phys.* 24(10): 663-672

Mari, A., Pacini, G., Murphy, E., Ludvik, B. and Nolan, J. J. 2001. A Model-Based Method for Assessing Insulin Sensitivity from the Oral Glucose Tolerance Test. *Diabetes Care.* 24(3): 539-548

McDonald, C., Dunaif, A. and Finegood, D. T. 2000. Minimal-Model Estimates of Insulin Sensitivity Are Insensitive to Errors in Glucose Effectiveness. *J Clin Endocrinol Metab.* 85(7): 2504-2508

McGuire, E. A., Tobin, J. D., Berman, M. and Andres, R. 1979. Kinetics of Native Insulin in Diabetic, Obese, and Aged Men. *Diabetes.* 28(2): 110-120

Mizock, B. A. 2001. Alterations in Fuel Metabolism in Critical Illness: Hyperglycaemia. *Best Pract Res Clin Endocrinol Metab.* 15(4): 533-551

Natali, A., Gastaldelli, A., Camastra, S., Sironi, A. M., Toschi, E., Masoni, A., Ferrannini, E. and Mari, A. 2000. Dose-Response Characteristics of Insulin Action on Glucose Metabolism: A Non-Steady-State Approach. *Am J Physiol Endocrinol Metab.* 278(5): E794-801

Parker, R. S. and Doyle, F. J., 3rd. 2001. Control-Relevant Modeling in Drug Delivery. *Adv Drug Deliv Rev.* 48(2-3): 211-228

Parker, R. S., Doyle, F. J., 3rd, Harting, J. and Peppas, N. A. (1996). Model Predictive Control for Infusion Pump Insulin Delivery. Proc *IEEE Conf on Eng in Med and Biology.* 1822-1823.

Pillonetto, G., Sparacino, G., Magni, P., Bellazzi, R. and Cobelli, C. 2002. Minimal Model S(I)=0 Problem in NIDDM Subjects: Nonzero Bayesian Estimates with Credible Confidence Intervals. *Am J Physiol Endocrinol Metab.* 282(3): E564-573

Prigeon, R. L., Roder, M. E., Porte, D., Jr. and Kahn, S. E. 1996. The Effect of Insulin Dose on the Measurement of Insulin Sensitivity by the Minimal Model Technique. Evidence for Saturable Insulin Transport in Humans. *J Clin Invest.* 97(2): 501-507

Radack, H. B. 1997. Sliding Scale Insulin Use. *Arch Intern Med.* 157(15): 1776

Sawin, C. T. 1997. Action without Benefit. The Sliding Scale of Insulin Use. *Arch Intern Med.* 157(5): 489

Segre, G., Turco, G. and Vercellone, G. 1973. Modeling Blood Glucose and Insulin Kinetics in Normal, Diabetic and Obese Subjects. *Diabetes.* 22: 94-103

Sherwin, R. S., Kramer, K. J., Tobin, J. D., Insel, P. A., Liljenquist, J. E., Berman, M. and Andres, R. 1974. A Model of the Kinetics of Insulin in Man. *J Clin Invest.* 53(5): 1481-1492

Skyler, J. S., Skyler, D. L., Seigler, D. E. and O'Sullivan, M. J. 1981. Algorithms for Adjustment of Insulin Dosage by Patients Who Monitor Blood Glucose. *Diabetes Care.* 4(2): 311-318

Sonksen, P. H., Tompkins, C. V., Srivastava, M. C. and Nabarro, J. D. 1973. A Comparative Study on the Metabolism of Human Insulin and Porcine Proinsulin in Man. *Clin Sci Mol Med.* 45(5): 633-654

Thorsteinsson, B. 1990. Kinetic Models for Insulin Disappearance from Plasma in Man. *Dan Med Bull.* 37(2): 143-153

Toffolo, G., Bergman, R. N., Finegood, D. T., Bowden, C. R. and Cobelli, C. 1980. Quantitative Estimation of Beta Cell Sensitivity to Glucose in the Intact Organism: A Minimal Model of Insulin Kinetics in the Dog. *Diabetes.* 29(12): 979-990

Trajanoski, Z. and Wach, P. 1998. Neural Predictive Controller for Insulin Delivery Using the Subcutaneous Route. *IEEE Trans Biomed Eng.* 45(9): 1122-1134

Turnheim, K. and Waldhausl, W. K. 1988. Essentials of Insulin Pharmacokinetics. *Wien Klin Wochenschr.* 100(3): 65-72

Vicini, P., Caumo, A. and Cobelli, C. 1997. The Hot IVGTT Two-Compartment Minimal Model: Indexes of Glucose Effectiveness and Insulin Sensitivity. *Am J Physiol.* 273(5 Pt 1): E1024-1032

Vicini, P., Caumo, A. and Cobelli, C. 1999. Glucose Effectiveness and Insulin Sensitivity from the Minimal Models: Consequences of Undermodeling Assessed by Monte Carlo Simulation. *IEEE Trans Biomed Eng.* 46(2): 130-137

Wilinska, M. E., Chassin, L. J., Schaller, H. C., Pieber, T. R. and Hovorka, R. (2003). Modelling Insulin Lispro Kinetics During Physiological Conditions in Subjects with Type 1 Diabetes Treated by CSII. Proc *World Congress on Biomedical Engineering and Medical Physics* in Sydney, Australia. 24-29 August 2003.

# 4

# PARAMETER VALUES

## 4.1 BACKGROUND

The concentration of glucose and insulin in the blood is a result of many processes, such as endogenous insulin secretion, exogenous insulin and glucose inputs, insulin and glucose distribution in the body, glucose and insulin interaction and utilisation, and storage of both insulin and glucose by organs in the body. Once a model is developed to include all these processes, the values of patient specific model parameters are the key element in obtaining good model fits and predictions, and must be physiologically justified and computationally optimised. In most physiological studies, each portion of the glucose-insulin system is analysed individually, but for a control model each of these individual portions must be combined.

The parameters used in the control model of Equations (3.19) – (3.20) are split into patient specific and generic parameters. For control modelling, patient specific parameters are determined by considering previously gathered data, either from the day before (Chase, et

al., 2003; Doran, et al., 2004a; 2004b), or immediately prior to fit, as presented later in this thesis. The patient specific parameters in the model make the generic system model unique to a particular patient. The generic parameters are based on reported results and held constant for all patients. This assumption reduces complexity in fitting, by assuming that the generic parameter is approximately the same throughout the population and does not significantly impact model performance.

The difficulty in model prediction using these values lies in the variability of glucose clearance, $p_G$, and insulin sensitivity, $S_I$, over time. Insulin sensitivity, $S_I$, can vary over a period of 3 – 24 hours (Wilinska, et al., 2003) in Type 1 diabetic individuals, and it is unknown whether this phenomenon occurs in critically ill patients. Glucose clearance, $p_G$, may also vary over time. In the critical care environment, the impact of a wide variety of pharmaceutical therapies, such as adrenaline-based vasopressors, must also be considered.

## 4.2 FRACTIONAL CLEARANCE OF GLUCOSE, $p_G$

The parameter $p_G$ determines the rate at which glucose is cleared from the system at basal insulin. It is a parameter that originated from the minimal model proposed by Bergman (1985) and is often referred to as $p_1$ or $S_G$. A number of researchers have used the minimal model to determine values for $p_G$, either empirically (Avogaro, et al., 1989; Bergman, et al., 1981; Cobelli, et al., 1999; McDonald, et al., 2000; Pillonetto, et al., 2002) or theoretically (Bettini, et al., 1995; Furler, et al., 1985; Vicini, et al., 1999), and have produced a wide range of values. Of the theoretical values listed in Table 4.1, Furler et al's (1985) estimates

encompass the entire range of those values proposed by others (0 – 0.028 $min^{-1}$). However, it should be noted that the value proposed by Furler et al (1985) for $p_G$ in Type 1 diabetic individuals, $p_G = 0$, results in instability in the minimal model as shown by the steady state analysis in Chapter 3. A zero value also implies absolutely no non-insulin mediated glucose clearance, which is not possible.

The values for $p_G$ from clinical studies also have a reasonably large range, spanning from 0.0059 $min^{-1}$ (Avogaro, et al., 1989) to 0.0466 $min^{-1}$ (Bergman, et al., 1981) and includes healthy, diabetic and obese individuals with varying levels of glucose tolerance. This range also encompasses ranges developed theoretically by a large margin. Unfortunately, the varying units and unknown assumptions made by Cobelli et al (1999), mean that converting their values to compare with other physiological values was not possible.

Although, the glucose effectiveness, $p_G$, may change over time, the variation is likely to be small compared with that of the insulin sensitivity, $S_I$ (McDonald, et al., 2000). The parameter for glucose effectiveness originated from the minimal model (Bergman, et al., 1985), and so it makes sense that use of the minimal model is most likely when determining a value for $p_G$ from the literature (e.g (Avogaro, et al., 1989; Bergman, et al., 1981; Bettini, et al., 1995; Cobelli, et al., 1999; McDonald, et al., 2000; Pillonetto, et al., 2002; Vicini, et al., 1999). The alternate model developed in Chapter 3 may have different values, although they are expected to be similar given the similarity of this model term to the minimal model. For this research a conservatively lower value of $p_G = 0.01$ $min^{-1}$ is assumed to be approximately normal for catabolic ICU patients, unless fitting dictates a different result.

TABLE 4.1: PHYSIOLOGICAL AND THEORETICAL VALUES FOR GLUCOSE CLEARANCE

| $S_G$ or $p_1$ or $p_G$ | Type | How Calculated? | Who? |
|---|---|---|---|
| 0.0059 – 0.0098 $min^{-1}$ | 6 Healthy | Minimal Model with Glucose Tracer | (Avogaro, et al., 1989) |
| 0.012 – 0.033 $min^{-1}$ | 6 Healthy | Minimal Model | (Avogaro, et al., 1989) |
| 0.0075 – 0.0101 $min^{-1}$ | 6 Healthy | Minimal Model with Glucose Tracer | (Avogaro, et al., 1989) |
| 0.0071 – 0.0246 $min^{-1}$ | 7 obese, low tolerance | Minimal Model | (Bergman, et al., 1981) |
| 0.0136 – 0.0217 $min^{-1}$ | 3 lean, low tolerance | Minimal Model | (Bergman, et al., 1981) |
| 0.0192 – 0.0464 $min^{-1}$ | 5 lean tolerant | Minimal Model | (Bergman, et al., 1981) |
| 0.0323 – 0.0466 $min^{-1}$ | 3 obese tolerant | Minimal Model | (Bergman, et al., 1981) |
| 0.0096 $min^{-1}$ | Theoretical Meal Hot | Minimal Model | (Bettini, et al., 1995) |
| 0.0098 $min^{-1}$ | Theoretical IVGTT Hot | Minimal Model | (Bettini, et al., 1995) |
| 0.0099 $min^{-1}$ | Theoretical Meal Cold | Minimal Model | (Bettini, et al., 1995) |
| 0.0243 $min^{-1}$ | Theoretical IVGTT Cold | Minimal Model | (Bettini, et al., 1995) |
| 2.81 ± 0.29 mL $min^{-1}$ $kg^{-1}$ | 22 IVGTT Normal | 2 compartment Minimal Model | (Cobelli, et al., 1999) |
| 4.27 ± 0.33 mL $min^{-1}$ $kg^{-1}$ | 22 IVGTT Normal | 1 Compartment Minimal Model | (Cobelli, et al., 1999) |
| 0 $min^{-1}$ | Type 1 proposed values | Minimal Model | (Furler, et al., 1985) |
| 0.028 $min^{-1}$ | Normal/ Insulin Resistant Proposed values | Minimal Model | (Furler, et al., 1985) |
| 0.008 – 0.038 $min^{-1}$ | 56 lean and obese women | Minimal Model | (McDonald, et al., 2000) |
| 0.0089-0.021 $min^{-1}$ | 10 NIDDM (Type 2) | Minimal Model | (Pillonetto, et al., 2002) |
| 0.010140 $min^{-1}$ $kg^{-1}$ | Simulated Data | Cold Minimal Model | (Vicini, et al., 1999) |
| 0.019864 $min^{-1}$ $kg^{-1}$ | Simulated Data | Cold Minimal Model | (Vicini, et al., 1999) |

## 4.3 INSULIN SENSITIVITY, $S_I$

Two-day proof of concept clinical trials using heavy derivative control (Chase, et al., 2003; Doran, et al., 2004a; 2004b) showed the need for an optimised insulin sensitivity parameter, $S_I$, that changed with time. Insulin sensitivity, $S_I$, is defined as the glucose responsiveness to the metabolic actions of exogenous and endogenous insulin and is the most important model parameter when automating insulin infusion. In-vivo insulin sensitivity may vary according to insulin concentration, exposure time, pulsatility and tissue delivery amoung others (Genuth, et al., 1998). The need for variation in insulin sensitivity is highly important in critically ill patients, as their physical state can often change quite quickly in response to stress of their condition, feeding, or medication.

A number of techniques have been developed to quantify insulin sensitivity or a surrogate measure. These techniques range in complexity and time required to obtain them. The simplest are scalar ratios, such as the HOMA (Katsuki, et al., 2001) and the QUICKI (Hrebicek, et al., 2002), which are the combination of fasting blood insulin and glucose values. These values are simple diagnostic tools for the extent of insulin resistance and are usually measured over a large population for comparisons of subgroups. The minimal model has been used by a number of researchers to find values of insulin sensitivity (e.g (Araujo-Vilar, et al., 1998; Avogaro, et al., 1989; Bergman, et al., 1981; 1987; Breda, et al., 2002; Caumo, et al., 1999; Cobelli, et al., 1999; Pacini and Bergman, 1986; Pillonetto, et al., 2002; Prigeon, et al., 1996; Vicini, et al., 1997; 1999). It is a more complex method and generally requires the patient to undergo a fasting period then an OGTT, FSIVTT or similar test, the whole process taking 8 hours or more. Computer simulations are then required to

determine the value of insulin sensitivity. The minimal model, in some forms, has been shown to underestimate insulin sensitivity (Cobelli, et al., 1999; Vicini, et al., 1999). The 'gold' standard for obtaining insulin sensitivity is the euglycemic clamp technique (DeFronzo, et al., 1979), however this test is labour and time intensive for both patients and clinicians, and hence is only suitable for more specialised clinical studies.

The majority of these methods calculate indices, which are used to indicate relative sensitivities, rather than an absolute value. Hence, while they are useful in comparing members of a clinical study and diagnosing insulin resistance or diabetes, they do not provide a value of insulin sensitivity, $S_I$, for the use in a control model. Only the intensive minimal model based methods and euglycemic clamp provide this physiological measure. Insulin sensitivity, $S_I$ or *ISI* (Insulin Sensitivity Index), has been a widely researched parameter, especially in the empirical sense as shown by the selection of insulin sensitivity values shown in the literature and presented in Table 4.2A and 4.2B.

TABLE 4.2A: PHYSIOLOGICAL VALUES FOR INSULIN SENSITIVITY

| $S_I$ or *ISI* | $S_I$* ($10^{-4}$) (L/mU/min) | Type | How Calculated? | Who? |
|---|---|---|---|---|
| $4.58 \pm 3.5 \times 10^{-5}$ $min^{-1}$ $(pmol\ L^{-1})^{-1}$ | 0.75 – 5.61 | Lean healthy | Modified Minimal Model | (Araujo-Vilar, et al., 1998) |
| $11.7 \pm 4.3 \times 10^{-5}$ $min^{-1}$ $(pmol\ L^{-1})^{-1}$ | 5.14 – 11.12 | Obese healthy | Modified Minimal Model | (Araujo-Vilar, et al., 1998) |
| $1.71 - 5.87 \times 10^{-4}$ $min^{-1}$ $\mu U^{-1}$ mL | 1.71 – 5.87 | 6 healthy (101±1% ideal body weight) | Minimal Model | (Avogaro, et al., 1989) |
| $2.23 - 8.20 \times 10^{-4}$ $min^{-1}$ $\mu U^{-1}$ mL | 2.23 – 8.20 | 6 healthy (101±1% ideal body weight) | Minimal Model with Glucose Tracer | (Avogaro, et al., 1989) |
| $3.17 - 5.13 \times 10^{-4}$ $min^{-1}$ $\mu U^{-1}$ mL | 3.17 – 5.13 | 6 healthy (101±1% ideal body weight) | Minimal Model with Glucose Tracer | (Avogaro, et al., 1989) |
| $7.83 \pm 5.3 \times 10^{-5}$ $min^{-1}$ $(pmol\ L^{-1})^{-1}$ | 1.76 – 6.12 | | MINIMOD 94 | Steil and Bergman 94 in (Araujo-Vilar, et al., 1998) |
| $5.1 \pm 1.3 \times 10^{-4}$ $min^{-1}$ $\mu U^{-1}$ mL | 3.8 – 6.4 | 5 lean, tolerant | Minimal Model | (Bergman, et al., 1981) |
| $4.9 \pm 1.0 \times 10^{-4}$ $min^{-1}$ $\mu U^{-1}$ mL | 3.9 – 5.9 | 3 lean, low tolerance | Minimal Model | (Bergman, et al., 1981) |
| $5.5 \pm 1.6 \times 10^{-4}$ $min^{-1}$ $\mu U^{-1}$ mL | 4.9 – 7.1 | 3 obese, tolerant | Minimal Model | (Bergman, et al., 1981) |
| $2.0 \pm 0.4 \times 10^{-4}$ $min^{-1}$ $\mu U^{-1}$ mL | 1.6 – 2.4 | 7 obese, low tolerance | Minimal Model | (Bergman, et al., 1981) |
| $0.037 \pm 0.007$ dL $min^{-1}$ $\mu U^{-1}$ mL | unsure | 10 normals | Clamps | (Bergman, et al., 1987) |
| $0.046 \pm 0.008$ dL $min^{-1}$ $\mu U^{-1}$ mL | unsure | 10 normals | FSIVTT | (Bergman, et al., 1987) |
| $11.67 \pm 1.71 \times 10^{-2}$ $min^{-1}$ $kg^{-1}$ mL | unsure | 22 IVGTT Normal | 2 Compartment Minimal Model | (Cobelli, et al., 1999) |
| $8.68 \pm 1.62 \times 10^{-2}$ $min^{-1}$ $kg^{-1}$ mL | unsure | 22 IVGTT Normal | 1 Compartment Minimal Model | (Cobelli, et al., 1999) |
| $13.08 \pm 1.17$ mg $min^{-1}$ $kg^{-1}$ $\mu U$ $mL^{-1}$ | unsure | 11 normals | Hyperglycemic clamp | (DeFronzo, et al., 1979) |

* Conversion is 0.144×pmol/L = mU/L

TABLE 4.2B: PHYSIOLOGICAL VALUES FOR INSULIN SENSITIVITY

| $S_I$ or $ISI$ | $S_I$* ($10^{-4}$) (L/mU/min) | Type | How Calculated? | Who? |
|---|---|---|---|---|
| $2.54 \pm 2.74$ $\mu U\ mL^{-1}\ min^{-1}$ | 0 – 5.28 | 18 Normals | Minimal Model of FSIVGTT | (Duncan, et al., 2003) |
| $4.41 \pm 3.30$ $\mu U\ mL^{-1}\ min^{-1}$ | 1.11 – 7.71 | 18 Normals | Minimal Model of FSIVGTT after exercise | (Duncan, et al., 2003) |
| $0.2 - 22.6 \times 10^{-4}$ $min^{-1}\ mU^{-1}\ mL$ | 0.2 – 22.6 | 56 lean and obese women | Minimal Model | (McDonald, et al., 2000) |
| $4.3 \pm 1.31$ $mL\ min^{-1}\ m^{-2}\ L^{-1}$ mU | 4.81 – 9.02*** | 4 lean healthy | Circulatory Model | (Natali, et al., 2000) |
| $1.25 \pm 0.07$ $mL\ min^{-1}\ m^{-2}\ L^{-1}$ mU | 2.28 – 2.55*** | 3 obese healthy | Circulatory Model | (Natali, et al., 2000) |
| $8.12 \pm 5.2 \times 10^{-5}$ $min^{-1}\ (pmol\ L^{-1})^{-1}$ | 2.03 – 9.25 | | MINIMOD 86 | (Pacini and Bergman, 1986) in (Araujo-Vilar, et al., 1998) |
| $0.6 - 2.1 \times 10^{-4}$ $min^{-1}\ mU^{-1}\ mL$ | 0.6 – 2.1 | 10 NIDDM (Type 2) | Minimal Model | (Pillonetto, et al., 2002) |
| $4.8 \pm 0.95 \times 10^{-5}$ $min^{-1}/pM$ | 4.62 – 6.90** | 7 obese | Bolus Injection, Peak Conc = 1167 ±156 pM | (Prigeon, et al., 1996) |
| $3.56 \pm 0.53 \times 10^{-5}$ $min^{-1}/pM$ | 3.64 – 4.91** | 7 obese | Bolus Injection, Peak Conc = 3014 ± 384 pM | (Prigeon, et al., 1996) |
| $2.42 \pm 0.40 \times 10^{-5}$ $min^{-1}/pM$ | 2.42 – 3.38 | 7 obese | Bolus Injection, Peak Conc = 6596 ± 547 pM | (Prigeon, et al., 1996) |
| $13.83 \pm 2.54 \times 10^{-2}$ $mL\ kg^{-1}\ min^{-1}\ \mu U^{-1}$ mL | unsure | 14 normal | 2 compartment minimal model | (Vicini, et al., 1997) |
| $12.98 \pm 2.21 \times 10^{-2}$ $mL\ kg^{-1}\ min^{-1}\ \mu U^{-1}$ mL | unsure | 14 normal | 2 compartment minimal model | (Vicini, et al., 1997) |

* Conversion is 0.144×pmol/L = mU/L

** 12 L distribution volume assumed

*** Using mean body surface area ($m^2$) (Natali, et al., 2000)

Theoretical values for insulin sensitivity, $S_I$, have also been proposed using the hot (with a tracer) and cold (no tracer) minimal model (Avogaro, et al., 1989; Caumo, et al., 1999; Vicini, et al., 1997). A selection of these values are shown in Table 4.3. The theoretical values range from $1.97 \times 10^{-4}$ to $5.2 \times 10^{-4}$ L/mU/min, while the empirical values range from 0 to $22.6 \times 10^{-4}$ L/mU/min, with the majority of values falling approximately in the range between $2 \times 10^{-4} - 8 \times 10^{-4}$ L/mU/min, as shown in Figure 4.1. It is interesting to note the wider empirical range, illustrating the significant variation encountered in clinical situations.

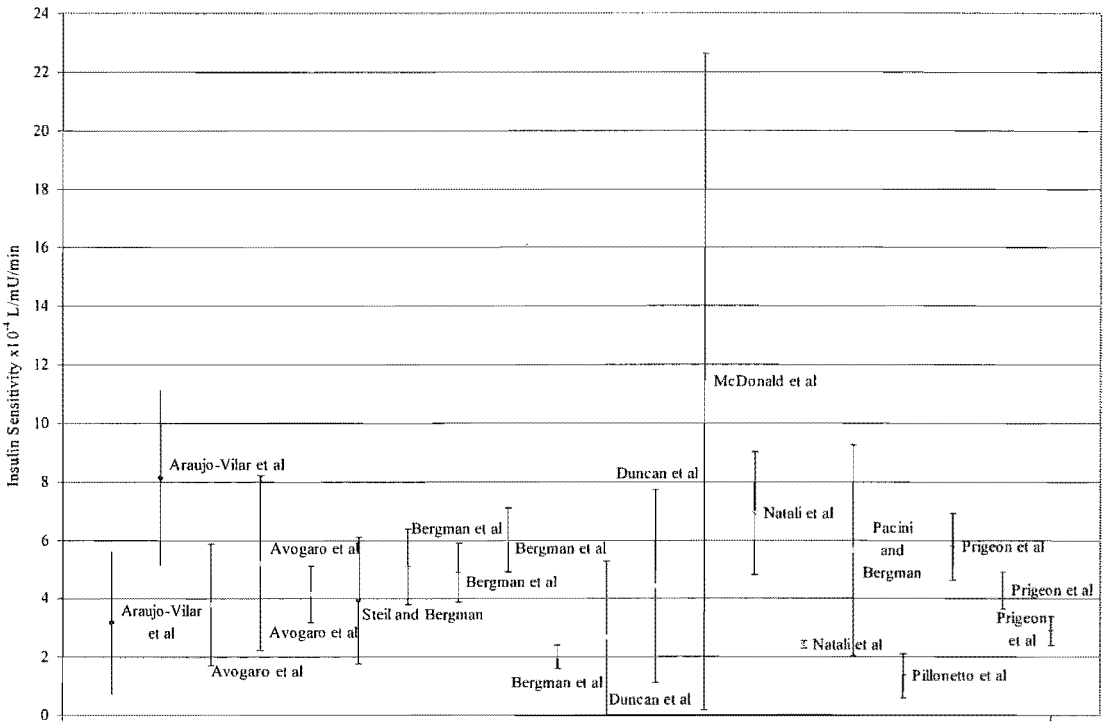


FIGURE 4.1: GRAPHICAL REPRESENTATION OF PHYSIOLOGICAL INSULIN SENSITIVITY VALUES

Insulin sensitivity is generally reduced for obese and diabetic individuals, and varies depending on the model or method used to obtain it. It should be noted, however, that

although insulin sensitivity varies, almost all values, excluding Araujo-Vilar et al (1998) and McDonald et al (2000), have the same order of magnitude. Finally, it should be noted that insulin sensitivity, $S_I$, exhibits a much larger range than the glucose clearance, $p_G$, illustrating its heavier impact on model results and potentially greater variability over time (McDonald, et al., 2000).

TABLE 4.3: THEORETICAL VALUES FOR INSULIN SENSITIVITY

| $S_I$ or ISI | Type | How Calculated? | Who? |
|---|---|---|---|
| $3.28 \times 10^{-4}$ $min^{-1}\ \mu U^{-1}\ mL$ | Theoretical IVGTT | Cold Minimal Model | (Bettini, et al., 1995) |
| $2.79 \times 10^{-4}$ $min^{-1}\ \mu U^{-1}\ mL$ | Theoretical Meal | Cold Minimal Model | (Bettini, et al., 1995) |
| $3.66 \times 10^{-4}$ $min^{-1}\ \mu U^{-1}\ mL$ | Theoretical IVGTT | Hot Minimal Model | (Bettini, et al., 1995) |
| $1.97 \times 10^{-4}$ $min^{-1}\ \mu U^{-1}\ mL$ | Theoretical Meal | Hot Minimal Model | (Bettini, et al., 1995) |
| $2.9 - 3.3 \times 10^{-4}$ $dL\ kg^{-1}\ min^{-1}\ \mu U^{-1}\ mL$ | Monte Carlo Simulations | Cold Minimal Model | (Caumo, et al., 1999) |
| $3.2 - 3.5 \times 10^{-4}$ $dL\ kg^{-1}\ min^{-1}\ \mu U^{-1}\ mL$ | Monte Carlo Simulations | Hot Minimal Model | (Caumo, et al., 1999) |
| $5.2 \times 10^{-4}$ $min^{-1}\ mU^{-1}\ L$ | Normal and Type 2 | Proposed values for Minimal Model | (Furler, et al., 1985) |
| $2 \times 10^{-4}$ $min^{-1}\ mU^{-1}\ L$ | Type 1 | Proposed values for Minimal Model | (Furler, et al., 1985) |
| $2.4 \times 10^{-4}$ $min^{-1}\ \mu U^{-1}\ mL$ | Simulated Data | Cold Minimal Model | (Vicini, et al., 1999) |
| $3.6 \times 10^{-4}$ $min^{-1}\ \mu U^{-1}\ mL$ | Simulated Data | Hot Minimal Model | (Vicini, et al., 1999) |

## 4.4 INTERSTITIAL INSULIN TRANSFER DELAY, *n*

The values for interstitial insulin transfer are calculated by considering the half-life of insulin as it travels through the interstitial fluid. The half-life, $t_{1/2}$ is easily converted to the interstitial insulin transfer delay, $n$, as shown in Figure 4.2.

$$0.5 = e^{-nt_{1/2}} \tag{4.1}$$

where:

$n$ = delay in interstitial transfer of insulin ($min^{-1}$)

$t_{1/2}$ = half-life of insulin in the interstitial space (min)

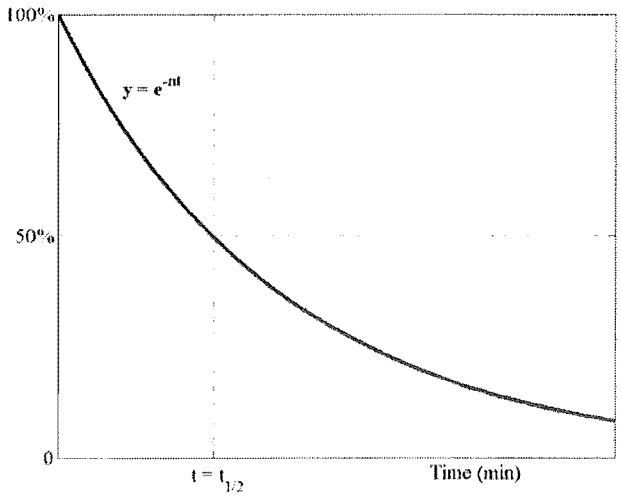


FIGURE 4.2: HALF-LIFE DECAY CURVE

A literature search for physiological values revealed the half-lives shown in Table 4.4. The intravascular space (i.e. in the blood vessels) has a much faster clearance, as shown by a lower half-life, than the interstitial space (i.e. in the small spaces between tissues and

organs). As expected, insulin infused intravenously was cleared faster than that infused subcutaneously. Initial trials used $n$ = 5/54 $min^{-1}$, a value obtained from Bergman et al (1985), which is equivalent to a half-life of approximately 7.5 min, which also falls within the range given by Thorsteinsson (1990) of a half-life of 4.6 – 8.3 min. From the physiological values of half-lives following an IV injection in Table 4.4 and advice from medical professionals the value of $n$ has been increased to $n$ = 0.16 $min^{-1}$, giving a half-life of approximately 4.3 minutes.

TABLE 4.4: PHYSIOLOGICAL VALUES FOR INTERSTITIAL TRANSFER HALF-LIFE

| $t_{1/2}$ (min) | $n$ ($min^{-1}$) | Where from? | Following | Who? |
|---|---|---|---|---|
| 1.5 | 0.46 | Low Affinity Insulin Binding Sites | After 12 hour infusion, bolus given, so insulin concentration is $10^{-8}$ M | (Nestler, et al., 1988) |
| 2.3 -2.4 | 0.29 - 0.30 | Intravascular space | IV injection | Silvers (1974) and Sherwin (1969) in (Turnheim and Waldhausl, 1988) |
| 2.4 | 0.29 | Intravascular space | IV injection | (Turnheim and Waldhausl, 1988) |
| 4.6 – 8.3 | 0.083 – 0.15 | Plasma (Interstitial) | IV injection | (Thorsteinsson, 1990) |
| 7.5 | 0.09 | | | (Bergman, et al., 1985) |
| 6 - 8 | 0.09 - 0.12 | High Affinity Insulin Binding Sites | 140 min after 12 hour infusion, bolus given so insulin concentration is $10^{-9}$ M | (Nestler, et al., 1988) |
| 14 | 0.04 | Interstitial fluid | IV injection | Silvers (1974) in (Turnheim and Waldhausl, 1988) |
| 8 - 24 | 0.03 - 0.09 | Pool 1 to Pool 2 | SC infusion | (Kraegen and Chisholm, 1984) |
| 25 ± 9 | 0.02 – 0.04 | Plasma (Interstitial) | 20mU/$m^2$/min for 0-100 min, then 200mU/$m^2$/min for 100-200 min (SC) | (Natali, et al., 2000) |

## 4.5 INSULIN DECAY HALF-LIFE, *k*

The values of interstitial insulin transfer are calculated by considering the half-life of insulin as it is removed from the interstitial fluid. The half-life, $t_{1/2}$ is easily converted to the insulin decay half-life, $k$.

$$0.5 = e^{-kt_{1/2}} \tag{4.2}$$

where:

$k$ = parameter controlling half-life of insulin decay ($min^{-1}$)

$t_{1/2}$ = half-life of insulin removal from the interstitial space (min)

The effect of changing $k$ is seen in Figure 4.3, where $t_{1/2}$ = 50 min corresponds to $k$ = 0.0139 $min^{-1}$, $t_{1/2}$ = 100 min corresponds to $k$ = 0.0069 $min^{-1}$ and $t_{1/2}$ = 150 min corresponds to $k$ = 0.0046 $min^{-1}$. It can be seen that as the half-life increases and $k$ decreases, that the rate of insulin removal is reduced, as expected.

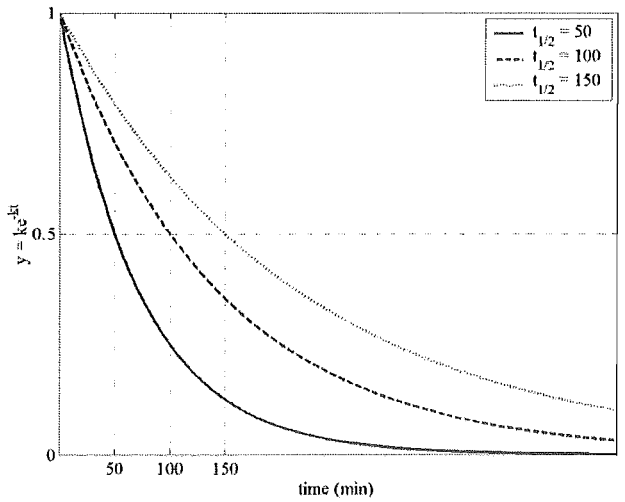


FIGURE 4.3: DECAY CURVES SHOWING THE EFFECT OF CHANGING INSULIN DECAY HALF-LIFE

TABLE 4.5: PHYSIOLOGICAL VALUES FOR INSULIN DECAY HALF-LIFE

| $t_{1/2}$ (min) | $k$ ($min^{-1}$) | Where From? | Following? | Who? |
|---|---|---|---|---|
| 53 | 0.0103 | Diabetics | CSII 3U/hr for 1 hour | (Kobayashi, et al., 1983) |
| 62 | 0.0112 | | 10mU/kg/min for 12-16 hours | (Nestler, et al., 1988) |
| 70 | 0.0099 | From Pool 2 | SC rapid 5 min infusion | (Kraegen and Chisholm, 1984) |
| 76 | 0.0091 | Radio labelled insulin | SC abdominal bolus | Joiner (1959) in (Kraegen and Chisholm, 1984) |
| 87 | 0.0080 | Radio labelled insulin | SC abdominal bolus | Binder (1969) in (Kraegen and Chisholm, 1984) |
| 50-130 | 0.0053 - 0.0139 | Elimination from the interstitial fluid and tissues that utilise insulin | IV injection | (Turnheim and Waldhausl, 1988) |
| 120 | 0.0058 | Radio labelled insulin | SC abdominal bolus | Karisto (1980) in (Kraegen and Chisholm, 1984) |
| 133 | 0.0052 | Tissues | IV injection | Silvers (1974) in (Turnheim and Waldhausl, 1988) |

Values shown in Table 4.5 considered the removal from the interstitial space following a subcutaneously injected insulin bolus. As the model developed in Chapter 3 is based on intravenously injected insulin, the half-life values given for a subcutaneous bolus are too long. Kraegen and Chisholm (1984) suggested that the delay in the subcutaneous layer is approximately 20 minutes. Thus, the range for half-lives of 50 – 130 minutes, with many values between 50 and 90 minutes leads to a value of $k = 0.0099$ $min^{-1}$ being selected, corresponding to a half-life of 70 minutes. This value was chosen to reflect the centroid of the values from the literature survey in Table 4.5.

## 4.6 SATURATION ON INSULIN TRANSPORTATION , $\alpha_I$

Saturation is assumed to follow Michaelis-Menten dynamics as discussed in Chapter 3.

$$K(C) = \frac{K_{max} C}{K_n + C} \tag{4.3}$$

where :

$K(C)$ = insulin action as a function of concentration

$K_{max}$ = maximal insulin disappearance rate via a saturable pathway

$K_n$ = plasma insulin concentration where insulin disappearance is half maximal

$C$ = plasma insulin concentration

In the model it is defined in Equation (3.14) and the specific term is repeated here.

$$K(I) = \frac{nI}{1+\alpha_I I} \tag{4.4}$$

where :

$K(I)$ = insulin action as a function of concentration

$n$ = delay in interstitial transfer of insulin ($min^{-1}$), where $n = K_{max}/K_n$

$\alpha_I$ = Michaelis-Menten parameter for saturation, where $\alpha_I = 1/K_n$

$I$ = plasma insulin concentration (mU/L)

TABLE 4.6: PHYSIOLOGICAL VALUES FOR INSULIN TRANSPORT SATURATION

| $K_{max}$ | $K_n$ | Clearance | Dose | Type? | Who? |
|---|---|---|---|---|---|
| 5.2 (4.0 – 9.1) nmol $min^{-1}$ | 2.7 (1.6 – 5.1) nmol $L^{-1}$ | 27.6 (17.3 – 47.9) mL $kg^{-1}$ $min^{-1}$ | 1 – 5 mU $kg^{-1}$ $min^{-1}$ | Normal | (Thorsteinsson, 1990) |
| 7.3 (6.6 – 8.9) nmol $min^{-1}$ | 3.9 (2.5 – 7.4) nmol $L^{-1}$ | 25.0 (18.6 – 47.1) mL $kg^{-1}$ $min^{-1}$ | 2-10 mU $kg^{-1}$ $min^{-1}$ | Normal | (Thorsteinsson, 1990) |
| 9.4 (6 – 12) nmol $min^{-1}$ | 7 (3.6 – 13) nmol $L^{-1}$ | 18 (10 – 23.7) mL $kg^{-1}$ $min^{-1}$ | 2-10 mU $kg^{-1}$ $min^{-1}$ | Type 1 | (Thorsteinsson, 1990) |
| | 2 nmol $L^{-1}$ | | | Normal | Jones (1984) in (Thorsteinsson, 1990) |
| | 0.0083 – 0.83[#] nmol $L^{-1}$ | | | Normal | Kuehn, 1980 in (Thorsteinsson, 1990) |
| | | 28.1 ± 8.3 mL $kg^{-1}$ $min^{-1}$ | | 18 Normal | (Thorsteinsson, 1990) |
| | | 28 mL $kg^{-1}$ $min^{-1}$ | | Normal | Shapiro (1987) in (Thorsteinsson, 1990) |
| | | 33.3 mL $kg^{-1}$ $min^{-1}$ | 0.2/0.5/0.9/1.8 mU $kg^{-1}$ $min^{-1}$ | 6 Normal | Frost (1979) in (Thorsteinsson, 1990) |
| | | 27.7 mL $kg^{-1}$ $min^{-1}$ | 2/4/6/8/10 mU $kg^{-1}$ $min^{-1}$ | 6 Normal | (Thorsteinsson, 1990) |
| | | 35.2 mL $kg^{-1}$ $min^{-1}$ | 1/2/3/4/5 mU $kg^{-1}$ $min^{-1}$ | 4 Normal | (Thorsteinsson, 1990) |
| 5.15[##] nmol $min^{-1}$ | | | | | (Baura, et al., 1993) |
| 6.15 ± 0.57 nmol $min^{-1}$ | 3.37 ± 0.28 nmol $L^{-1}$ | 24.9 ± 1.7 mL $kg^{-1}$ $min^{-1}$ | 1/2/3/4/5 mU $kg^{-1}$ $min^{-1}$ | 8 Normal | (Ellemann, et al., 1987) |
| | | | 1/2/3/4/5 mU $kg^{-1}$ $min^{-1}$ | 8 Cortisone | (Ellemann, et al., 1987) |
| | | 19 mL $kg^{-1}$ $min^{-1}$ | 0.13/0.2/0.4 mU $kg^{-1}$ $min^{-1}$ | Normal | (Thorsteinsson, et al., 1986) |

[#] Assuming a 12 L distribution volume, ## Conversion from μU, nmol/min = μU/min/$(0.144\times10^{-6})$

Table 4.6 shows the values from the literature, which are mainly from Thorteinsson's work (1990). Table 4.7 shows the calculated values calculated using Equation (4.4). Note also that $n$ is very similar to that shown in Table 4.4, despite the independent calculation.

The range of physiological values for the insulin saturation parameter, $\alpha_I$, range from 0.0005 – 0.0043 L/mU. The value used in this research is $\alpha_I = 1.7 \times 10^{-3}$ L/mU, which lies approximately in the centre of the ranges found by Thorsteinsson (1990) for normal subjects. It is currently unknown if a critically ill patient has a significantly different saturation level, and hence the value for normal subjects was chosen.

TABLE 4.7: CALCULATED PARAMETERS FOR INSULIN SATURATION

| $K_{max}$ | $K_n$ | $n^+$ ($min^{-1}$) | $\alpha_I^{++}$ (L/mU) | Type? | Who? |
|---|---|---|---|---|---|
| 5.2 (4.0 – 9.1) nmol $min^{-1}$ | 2.7 (1.6 – 5.1) nmol $L^{-1}$ | 0.16 | 0.0026 (0.0014 – 0.0043) | Normal | (Thorsteinsson, 1990) |
| 7.3 (6.6 – 8.9) nmol $min^{-1}$ | 3.9 (2.5 – 7.4) nmol $L^{-1}$ | 0.16 | 0.0018 (0.0009 - 0.0028) | Normal | (Thorsteinsson, 1990) |
| 9.4 (6 – 12) nmol $min^{-1}$ | 7 (3.6 – 13) nmol $L^{-1}$ | 0.11 | 0.0009 (0.0005 - 0.0019) | Type 1 | (Thorsteinsson, 1990) |
| | 2 nmol $L^{-1}$ | | 0.0035 | Normal | Jones (1984) in (Thorsteinsson, 1990) |
| 6.15 ± 0.57 nmol $min^{-1}$ | 3.37 ± 0.28 nmol $L^{-1}$ | 0.15 | 0.0019 – 0.0022 | 8 Normal | (Ellemann, et al., 1987) |

$^+$ Assuming a distribution volume of 12 L, $^{++}$ Conversion L/mU = L/nmol/144

## 4.7 SATURATION ON FRACTIONAL CLEARANCE OF GLUCOSE, $\alpha_G$

Although, the fractional clearance of glucose is primarily controlled by the insulin sensitivity parameter, $S_I$, which links exogenous insulin and endogenous glucose levels, a number of investigators (Duckworth and Kitabchi, 1981; Natali, et al., 2000; Nestler, et al., 1988; Prigeon, et al., 1996; Transberg, et al., 1981; Turnheim and Waldhausl, 1988) have examined glucose response to varying insulin dose. Overall, as the dose of exogenous insulin is increased insulin sensitivity, $S_I$, decreases (Prigeon, et al., 1996). This result occurs because of insulin saturation at the receptor site, affecting the rate of glucose clearance (Natali, et al., 2000).

Literature searches for levels of saturation showed that the number of researchers to investigate this phenomenon is reasonably small, as seen in Table 4.8. The Michaelis-Menten value of saturation, $\alpha_G$, is the value $1/K_n$ shown in Table 4.8, where Natali et al (2000) is the primary researcher. As Natali et al (2000) uses a circulatory model of glucose and insulin kinetics, their insulin sensitivity is based on tracer measurements, a hot index, and is consequently much larger than values of insulin sensitivity used for the minimal model. As there is a trade-off between the fractional glucose clearance saturation, $\alpha_G$, and the insulin sensitivity parameter, $S_I$, an initial generic value of $\alpha_G = 0.04$, was used across all patients.

TABLE 4.8: PHYSIOLOGICAL VALUES FOR GLUCOSE CLEARANCE SATURATION

| $K_{max}$ | $K_n$ | Clearance | Dose | Type | Who |
|---|---|---|---|---|---|
| | | $214 \pm 29$ mL $m^{-2}$ $min^{-1}$ | | Normal | (Nestler, et al., 1988) |
| | | 14 – 35 mL $kg^{-1}$ $min^{-1}$ | 8.2 – 43.3 mU $kg^{-1}$ | Normal | (Transberg, et al., 1981) |
| | 81 – 443 mU $L^{-1}$ | 570 – 771 mL $m^{-2}$ $min^{-1}$ | 20/200 mU $m^{-2}$ $min^{-1}$ | 4 Lean | (Natali, et al., 2000) |
| | 414 – 1122 mU $L^{-1}$ | 536 – 1332 mL $m^{-2}$ $min^{-1}$ | 20/200 mU $m^{-2}$ $min^{-1}$ | 3 Obese | (Natali, et al., 2000) |
| | | 700 – 800 mL $min^{-1}$ | | | (Turnheim and Waldhausl, 1988) |
| $2 – 5 \times 10^{-7}$ M | | | | | (Duckworth and Kitabchi, 1981) |

Following clinical trials and model validation with retrospective data, the initial estimate of $\alpha_G = 0.04$ was found to be too high, and hence saturating glucose clearance in the model when it was not saturating in the patient. The estimate was reduced to $\alpha_G = 0.015$ following additional literature searches revealing values in the range 0.015 – 0.025 (Caumo, et al., 1999; Prigeon, et al., 1996; Rizza, et al., 1981). The lower end of this range was chosen as a conservative estimate as this choice improves patient safety when used for clinical control. More specifically, if the patient's glucose clearance saturates below this level the blood glucose will not drop as far for a given (saturating) insulin input.

## 4.8 SUMMARY

The use of previously determined parameters from an extensive literature search has reduced the number and range of clinical trials that have to be completed to determine physiologically valid model parameters. The complexities of the glucose insulin system means responses have to be studied in smaller subsections and then combined to give the parameters required for a system model. The literature survey results outlined here form the basis of both ranges of patient specific models and initial estimates for generic patient values. These values are then refined through clinical studies and model fitting retrospectively to determine their ability to allow the system model developed to effectively mimic the human glucose-insulin metabolism.

## 4.9 REFERENCES

Araujo-Vilar, D., Rega-Liste, C. A., Garcia-Estevez, D. A., Sarmiento-Escalona, F., Mosquera-Tallon, V. and Cabezas-Cerrato, J. 1998. Minimal Model of Glucose Metabolism: Modified Equations and Its Application in the Study of Insulin Sensitivity in Obese Subjects. *Diabetes Res Clin Pract.* 39(2): 129-141

Avogaro, A., Bristow, J. D., Bier, D. M., Cobelli, C. and Toffolo, G. 1989. Stable-Label Intravenous Glucose Tolerance Test Minimal Model. *Diabetes.* 38(8): 1048-1055

Baura, G. D., Foster, D. M., Porte, D., Jr., Kahn, S. E., Bergman, R. N., Cobelli, C. and Schwartz, M. W. 1993. Saturable Transport of Insulin from Plasma into the Central Nervous System of Dogs in Vivo. A Mechanism for Regulated Insulin Delivery to the Brain. *J Clin Invest.* 92(4): 1824-1830

Bergman, R. N., Finegood, D. T. and Ader, M. 1985. Assessment of Insulin Sensitivity in Vivo. *Endocr Rev.* 6(1): 45-86

Bergman, R. N., Phillips, L. S. and Cobelli, C. 1981. Physiologic Evaluation of Factors Controlling Glucose Tolerance in Man: Measurement of Insulin Sensitivity and Beta-Cell Glucose Sensitivity from the Response to Intravenous Glucose. *J Clin Invest.* 68(6): 1456-1467

Bergman, R. N., Prager, R., Volund, A. and Olefsky, J. M. 1987. Equivalence of the Insulin Sensitivity Index in Man Derived by the Minimal Model Method and the Euglycemic Glucose Clamp. *J Clin Invest.* 79(3): 790-800

Bettini, F., Caumo, A. and Cobelli, C. (1995). Minimal Models in Meal-Like Protocols: Simulation Studies to Assess Precision and Physiological Plausibility of Parameter Estimates. Proc *IEEE 17th Annual Conference.* 20-23 Sept. 1995. 1361-1362.

Breda, E., Toffolo, G., Polonsky, K. S. and Cobelli, C. 2002. Insulin Release in Impaired Glucose Tolerance: Oral Minimal Model Predicts Normal Sensitivity to Glucose but Defective Response Times. *Diabetes.* 51 Suppl 1: S227-233

Caumo, A., Vicini, P., Zachwieja, J. J., Avogaro, A., Yarasheski, K., Bier, D. M. and Cobelli, C. 1999. Undermodeling Affects Minimal Model Indexes: Insights from a Two-Compartment Model. *Am J Physiol.* 276(6 Pt 1): E1171-1193

Chase, J. G., Shaw, G. M., Doran, C. V., Hudson, N. H. and Moorhead, K. T. (2003). Derivative Weighted Active Insulin Control Algorithms and Trials. Proc *IFAC Symposium* in Melbourne, Australia.

Cobelli, C., Caumo, A. and Omenetto, M. 1999. Minimal Model SG Overestimation and SI Underestimation: Improved Accuracy by a Bayesian Two-Compartment Model. *Am J Physiol.* 277(3 Pt 1): E481-488

DeFronzo, R. A., Tobin, J. D. and Andres, R. 1979. Glucose Clamp Technique: A Method for Quantifying Insulin Secretion and Resistance. *Am J Physiol.* 237(3): E214-223

Doran, C. V., Chase, J. G., Shaw, G. M., Moorhead, K. T. and Hudson, N. H. 2004a. Automated Insulin Infusion Trials in the ICU. *Diabetes Technology and Therapeutics.* 6(2)

Doran, C. V., Moorhead, K. T., Hudson, N. H., Chase, J. G. and Shaw, G. M. 2004b. Derivative Weighted Active Insulin Control Modelling and Clinical Trials for ICU Patients. *Med Eng Phys.* -to appear

Duckworth, W. C. and Kitabchi, A. E. 1981. Insulin Metabolism and Degradation. *Endocr Rev.* 2(2): 210-233

Duncan, G. E., Perri, M. G., Theriaque, D. W., Hutson, A. D., Eckel, R. H. and Stacpoole, P. W. 2003. Exercise Training, without Weight Loss, Increases Insulin Sensitivity and Postheparin Plasma Lipase Activity in Previously Sedentary Adults. *Diabetes Care.* 26(3): 557-562

Ellemann, K., Thorsteinsson, B., Fugleberg, S., Feldt-Rasmussen, B., Andersen, O. O., Gronbaek, P. and Binder, C. 1987. Kinetics of Insulin Disappearance from Plasma in Cortisone-Treated Normal Subjects. *Clin Endocrinol (Oxf).* 26(5): 623-628

Furler, S. M., Kraegen, E. W., Smallwood, R. H. and Chisholm, D. J. 1985. Blood Glucose Control by Intermittent Loop Closure in the Basal Mode: Computer Simulation Studies with a Diabetic Model. *Diabetes Care.* 8(6): 553-561

Genuth, S., Brownlee, M., Kuller, L., Samols, E., Saudek, C. and Sherwin, R. 1998. Consensus Development Conference on Insulin Resistance. *Diabetes Care.* 22(2): 310-315

Hrebicek, J., Janout, V., Malincikova, J., Horakova, D. and Cizek, L. 2002. Detection of Insulin Resistance by Simple Quantitative Insulin Sensitivity Check Index QUICKI for Epidemiological Assessment and Prevention. *J Clin Endocrinol Metab.* 87(1): 144-147

Katsuki, A., Sumida, Y., Gabazza, E. C., Murashima, S., Furuta, M., Araki-Sasaki, R., Hori, Y., Yano, Y. and Adachi, Y. 2001. Homeostasis Model Assessment Is a Reliable Indicator of Insulin Resistance During Follow-up of Patients with Type 2 Diabetes. *Diabetes Care.* 24(2): 362-365

Kobayashi, T., Sawano, S., Itoh, T., Kosaka, K., Hirayama, H. and Kasuya, Y. 1983. The Pharmacokinetics of Insulin after Continuous Subcutaneous Infusion or Bolus Subcutaneous Injection in Diabetic Patients. *Diabetes.* 32(4): 331-336

Kraegen, E. W. and Chisholm, D. J. 1984. Insulin Responses to Varying Profiles of Subcutaneous Insulin Infusion: Kinetic Modelling Studies. *Diabetologia.* 26(3): 208-213

McDonald, C., Dunaif, A. and Finegood, D. T. 2000. Minimal-Model Estimates of Insulin Sensitivity Are Insensitive to Errors in Glucose Effectiveness. *J Clin Endocrinol Metab.* 85(7): 2504-2508

Natali, A., Gastaldelli, A., Camastra, S., Sironi, A. M., Toschi, E., Masoni, A., Ferrannini, E. and Mari, A. 2000. Dose-Response Characteristics of Insulin Action on Glucose Metabolism: A Non-Steady-State Approach. *Am J Physiol Endocrinol Metab.* 278(5): E794-801

Nestler, J. E., Clore, J. N. and Blackard, W. G. 1988. Reduced Insulin Clearance in Normal Subjects Due to Extreme Hyperinsulinemia. *Am J Med Sci.* 295(1): 15-22

Pacini, G. and Bergman, R. N. 1986. Minmod: A Computer Program to Calculate Insulin Sensitivity and Pancreatic Responsivity from the Frequently Sampled Intravenous Glucose Tolerance Test. *Comput Methods Programs Biomed.* 23(2): 113-122

Pillonetto, G., Sparacino, G., Magni, P., Bellazzi, R. and Cobelli, C. 2002. Minimal Model S(I)=0 Problem in NIDDM Subjects: Nonzero Bayesian Estimates with Credible Confidence Intervals. *Am J Physiol Endocrinol Metab.* 282(3): E564-573

Prigeon, R. L., Roder, M. E., Porte, D., Jr. and Kahn, S. E. 1996. The Effect of Insulin Dose on the Measurement of Insulin Sensitivity by the Minimal Model Technique. Evidence for Saturable Insulin Transport in Humans. *J Clin Invest.* 97(2): 501-507

Rizza, R. A., Mandarino, L. J. and Gerich, J. E. 1981. Dose-Response Characteristics for Effects of Insulin on Production and Utilization of Glucose in Man. *Am J Physiol.* 240(6): E630-639

Thorsteinsson, B. 1990. Kinetic Models for Insulin Disappearance from Plasma in Man. *Dan Med Bull.* 37(2): 143-153

Thorsteinsson, B., Fugleberg, S. and Binder, C. 1986. Non-Linearity of Insulin Kinetics. *Diabetologia.* 29(12): 898

Transberg, K., Hagander, P. and Thorell, J. 1981. Disappearance of Insulin in Man: Variation with the Plasma Insulin Level. *Acta Endocrinol (Copenh).* 97: 391-397

Turnheim, K. and Waldhausl, W. K. 1988. Essentials of Insulin Pharmacokinetics. *Wien Klin Wochenschr.* 100(3): 65-72

Vicini, P., Caumo, A. and Cobelli, C. 1997. The Hot IVGTT Two-Compartment Minimal Model: Indexes of Glucose Effectiveness and Insulin Sensitivity. *Am J Physiol.* 273(5 Pt 1): E1024-1032

Vicini, P., Caumo, A. and Cobelli, C. 1999. Glucose Effectiveness and Insulin Sensitivity from the Minimal Models: Consequences of Undermodeling Assessed by Monte Carlo Simulation. *IEEE Trans Biomed Eng.* 46(2): 130-137

Wilinska, M. E., Chassin, L. J., Schaller, H. C., Pieber, T. R. and Hovorka, R. (2003). Modelling Insulin Lispro Kinetics During Physiological Conditions in Subjects with Type 1 Diabetes Treated by CSII. Proc *World Congress on Biomedical Engineering and Medical Physics* in Sydney, Australia. 24-29 August 2003.

# 5

# PARAMETER IDENTIFICATION

## 5.1 MOTIVATION

For the system model to be useful for real-time control, an efficient method of identifying patient specific parameters in clinical real-time is required. Objectives include low computation time, high accuracy for tracking changes in patient specific parameters, $p_G$ and $S_I$, and physiologically realistic values of optimised parameters. A method that is convex and not dependent on starting point, as with non-linear recursive least squares (Hovorka and Vicini, 2001), is also desirable. The model developed in Chapter 3 is presented here for review.

$$\dot{G} = -p_G G - S_I (G + G_B) \frac{Q}{1 + \alpha_G Q} + P(t) \tag{5.1}$$

$$\dot{Q} = -kQ + kI \tag{5.2}$$

$$\dot{I} = -\frac{nI}{1 + \alpha_I I} + \frac{u(t)}{V_I} + \frac{e^{(-u(t))} I_B}{V_I} \tag{5.3}$$

## 5.2 METHOD

Parameter values from the literature are presented in Table 5.1. The exogenous feed details are known, so the value of the exogenous glucose infusion, $P(t)$, can be determined. The equilibrium glucose level, $G_E$, can be estimated, either using the initial value for a short term trial or by averaging the glucose readings across the prior 12 hours for longer data fitting.

TABLE 5.1: GENERIC SYSTEM MODEL PARAMETERS

| Parameter | Value |
|---|---|
| $V_I$ | 12 L |
| $n$ | 0.16 $min^{-1}$ |
| $k$ | 0.0099 $min^{-1}$ |
| $\alpha_G$ | 0.04 |
| $\alpha_I$ | $1.7 \times 10^{-3}$ |

Comparisons between gathered data and the system model output are done by minimising the $L_2$ norm between measured data and model parameters. Initially, blood glucose data is approximated as a continuous series, using a simple linear approximation to form a piecewise linear curve, $G_{approx}$. The patient specific parameters, $p_G$ and $S_I$, are then defined as piecewise constants over the time series of the measured data.

$$p_G = \sum_{i=1}^{N} (p_{Gi}(H(t-120*(i-1)) - H(t-120i)) \tag{5.4}$$

$$S_I = \sum_{i=1}^{N} (S_{Ii}(H(t-120*(i-1)) - H(t-120i)) \tag{5.5}$$

where $H(t - t_0)$ is the Heaviside function defined by $H(t - t_0) = 0$ when $t$ is less than $t_0$, and $H(t - t_0) = 1$, when $t$ is greater than or equal to $t_0$. Note that $N$ in Equations (5.4) and (5.5) may be different depending on the number of hours per segment. For this research, the fractional clearance of glucose, $p_G$, is held constant over two hour periods and the insulin sensitivity, $S_I$, varies every hour, creating piecewise constant time varying model parameters. Note that the variation in Equations (5.4) – (5.5) can also be defined as linear, or higher order, over these time periods for greater detail.

The next step is to optimise the parameter values. For any glucose model output curve that is a solution to Equation (5.1), the following expression holds for any period of time between $t$ and $t_0$:

$$\int_0 \dot{G}\,dt = \int_0 (-p_G G - S_I(G + G_B)Q + P(t))\,dt \tag{5.6}$$

Equation (5.6) can be re-written:

$$G(t) - G(t_0) + \int_0 p_G G(t)\,dt + \int_0 S_I(G(t) + G_e)Q(t)\,dt - \int_0 P(t)dt = 0 \tag{5.7}$$

It should be noted that the glucose level, $G$, is defined as the glucose level above the equilibrium glucose level, $G_E$. Hence, the measured glucose level, $\tilde{G}$, is actually $G + G_E$, resulting in a equivalent expression.

$$\tilde{G}(t) - \tilde{G}(t_0) + \int_0 p_G(\tilde{G}(t) - G_E)\,dt + \int_0 S_I \tilde{G}(t)Q(t)\,dt - \int_0 P(t)dt = 0 \tag{5.8}$$

An important aspect of any parameter fit is the resulting error in the fit. Let $\tilde{G}_{fit}$ be the best fit from the model to the measured data, with corresponding piecewise constant functions for patient specific parameters, $p_G^{fit}$ and $S_I^{fit}$. Consider also a time interval, $[t_0, t]$, where for $t_0 < t < t_1$, the patient specific parameter values from the best fit to the measured data, $p_G^{fit}$ and $S_I^{fit}$, are constant over that period with values represented by $\bar{p}_G$ and $\bar{S}_I$, respectively. Then the best fit of the model is equal to sum of the simple linear approximation and an error term, $\varepsilon(t)$:

$$\tilde{G}_{fit}(t) = \tilde{G}_{approx}(t) + \varepsilon(t) \tag{5.9}$$

where the error term, $\varepsilon(t)$, falls within the interval, $0 \le |\varepsilon(t)| \le \delta$, for small $\delta$. The best fit of the model at any time, $\tilde{G}_{fit}(t)$, is calculated:

$$\begin{aligned}\tilde{G}_{fit}(t) &= \tilde{G}_{fit}(t_0) - \bar{p}_G \int_0 (\tilde{G}_{fit}(t) - G_e)\,dt - \bar{S}_I \int_0 \tilde{G}_{fit}(t) Q(t)\,dt + \int_0 P(t)\,dt \\ &= \tilde{G}_{approx}(t_0) + \bar{p}_G (t - t_0) G_e - \bar{p}_G \int_0 \tilde{G}_{approx}(t)\,dt - \bar{S}_I \int_0 \tilde{G}_{approx}(t) Q(t)\,dt + \int_0 P(t)\,dt + E(t)\end{aligned} \tag{5.10}$$

where the error term, $E(t)$, is defined:

$$\begin{aligned}|E(t)| &= |\varepsilon(t_0) - \bar{p}_G \int_0 \varepsilon(t)\,dt - \bar{S}_I \int_0 \varepsilon(t) Q(t)\,dt| \\ &\le |\varepsilon(t_0)| + \bar{p}_G \left| \int_0 \varepsilon(t)\,dt \right| + \bar{S}_I \left| \int_0 \varepsilon(t) Q(t)\,dt \right| \\ &\le \delta + \bar{p}_G \int_0 |\varepsilon(t)|\,dt + \bar{S}_I \int_0 |\varepsilon(t)| Q(t)\,dt \\ &\le \delta + \bar{p}_G \delta (t - t_0) + \bar{S}_I \delta \int_0 Q(t)\,dt \\ &= O(\delta)\end{aligned} \tag{5.11}$$

Note than even if the time period, $t - t_0$, and the convolution integral, $\int_0 Q(t)dt$, are both large, then the piecewise patient specific parameter terms, $\bar{p}_G\delta(t-t_0)$ and $\bar{S}_I\delta\int_0 Q(t)dt$, are small compared to the integral patient specific terms, $\bar{p}_G\int_0 \tilde{G}_{fit}(t)dt$ and $\bar{S}_I\int_0 \tilde{G}_{fit}(t)Q(t)dt$, when it is assumed that the best fit to the glucose data is greater than 1, $\tilde{G}_{fit}(t) > 1$, since:

$$\left|\frac{\bar{p}_G\delta(t-t_0)}{\bar{p}_G\int_0 \tilde{G}_{fit}(t)dt}\right| < \frac{\delta(t-t_0)}{\int_0 1dt} = \delta \tag{5.12}$$

$$\left|\frac{\bar{S}_I\delta\int_0 Q(t)dt}{\bar{S}_I\int_0 \tilde{G}_{fit}(t)Q(t)dt}\right| < \frac{\delta\int_0 Q(t)dt}{\int_0 Q(t)dt} = \delta \tag{5.13}$$

Thus, for a general time period $[t_0, t]$ an approximation can be used to represent the best fit, $\tilde{G}_{fit}(t)$, utilising integral functions.

$$\tilde{G}^{approx}_{model}(t) = \tilde{G}_{approx}(t_0) - \int_0 p_G(\tilde{G}_{approx}(t) - G_e)dt - \int_0 S_I\tilde{G}_{approx}(t)Q(t)dt + \int_0 P(t)dt \tag{5.14}$$

Integral functions have the advantage that they are insensitive to noise in the measured glucose data effectively providing a low-pass filter in the summations involved in numerically integrating.

For example, when the length of the time period is chosen to be 120 minutes long, [$t_0$, $t_0$ + 120], the fractional clearance of glucose, $p_G$, takes on one value, $p_{G1}$, and the insulin sensitivity parameter, $S_I$, takes on two values, $S_{I1}$ and $S_{I2}$, giving three unknowns for this time period. To find the values of these patient specific parameters that give the best fit to the measured glucose data in this time interval, six equations are proposed with a generic form:

$$\widetilde{G}_{approx}(t_0+20i)-\widetilde{G}_{fit}^{approx}(t_0+20i)=0,\quad i=1\ldots6 \tag{5.15}$$

To show the form that ensues the first and last of these equations, $i$ = 1 and $i$ = 6, are given:

$$\begin{aligned}&\widetilde{G}_{approx}(t_0+20)-\widetilde{G}_{approx}(t_0)-20\bar{p}_{G_1}G_e+\bar{p}_{G_1}\int_0^{t_0+20}\widetilde{G}_{approx}(t)\,dt\\&+\bar{S}_{I_1}\int_0^{t_0+20}\widetilde{G}_{approx}(t)Q(t)\,dt-\int_0^{t_0+20}P(t)\,dt=0\end{aligned} \tag{5.16}$$

$$\begin{aligned}&\widetilde{G}_{approx}(t_0+120)-\widetilde{G}_{approx}(t_0)-120\bar{p}_{G_1}G_e+\bar{p}_{G_1}\int_0^{t_0+120}\widetilde{G}_{approx}(t)\,dt\\&+\bar{S}_{I_1}\int_0^{t_0+60}\widetilde{G}_{approx}(t)Q(t)\,dt+\bar{S}_{I_2}\int_{t_0+60}^{t_0+120}\widetilde{G}_{approx}(t)Q(t)\,dt-\int_0^{t_0+120}P(t)\,dt=0\end{aligned} \tag{5.17}$$

where the integrals in Equations (5.16) and (5.17) can be quite easily evaluated numerically. The unknowns in these equations are $p_{G1}$, and $S_{I1}$ and $S_{I2}$. Therefore, for $i$ = 1…6, Equation 5.15 defines a simple least squares system of six linear equations with three unknowns.

To illustrate, blood glucose measurement data recorded for a critical care patient over 6.5 days is shown by the dots and error bars in Figure 5.1. This data is then broken into 120

minute intervals producing 462 equations with 231 unknowns. The equilibrium glucose level, $G_E$, is recalculated every 12 hours. The 462 equations for all these intervals are solved by constrained linear least squares in MATLAB where the patient specific parameters, $p_G$ and $S_I$, are limited to within the ranges, $0.01 \leq p_G \leq 0.02$ and $0.00001 \leq S_I \leq 0.0025$, respectively. The values of the patient specific parameters, $p_G$ and $S_I$, are used to solve the differential equation shown in Equation (5.6) over the 6.4 day interval. The line in Figure 5.1 shows a very close model fit to the data, however the insulin sensitivity, $S_I$, shown in Figure 5.2 has undesirable, non-physiological sudden jumps. This result is due to noise in the glucose measurements which is transferred, via the model and fit, to noise in both $p_G$ and $S_I$. To further reduce the noise, each $p_G$ and $S_I$ value is replaced by its 3-point moving average value, filtering out the impact of noise and possibility of erroneous measurements, such as the very low minimum value at approximately $t = 1.75$ days.

The fit using smoothed patient parameters shown in Figure 5.3 is an excellent fit over the 6.4 days the patient was studied. This accuracy shows that the dynamics in the model are easily capable of capturing patient dynamics for extended periods with physiologically realistic conditions and the fitting approach based on the use of integration, reduces the noise in the data. By using linear regression, the resulting equations are a well-posed, convex problem that is easily solved and is not starting point dependent like the commonly used non-linear recursive least squares method (Hovorka and Vicini, 2001). The result is a numerically simple optimisation routine suitable for use in clinical situations, particularly where real-time control applications are required.

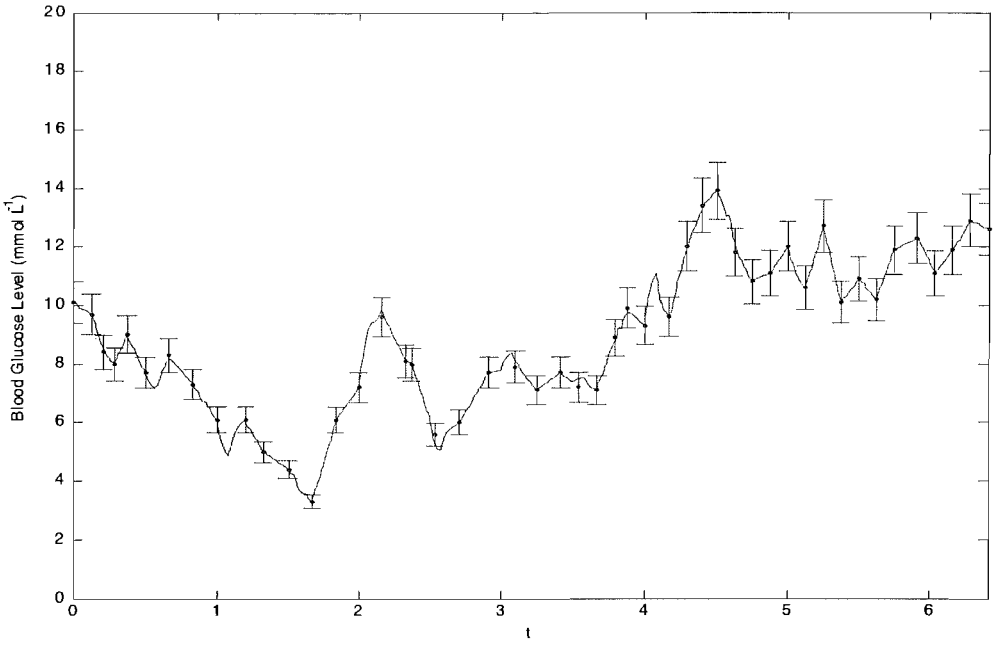


FIGURE 5.1: AN EXAMPLE BLOOD GLUCOSE DATA AND INITIAL FIT

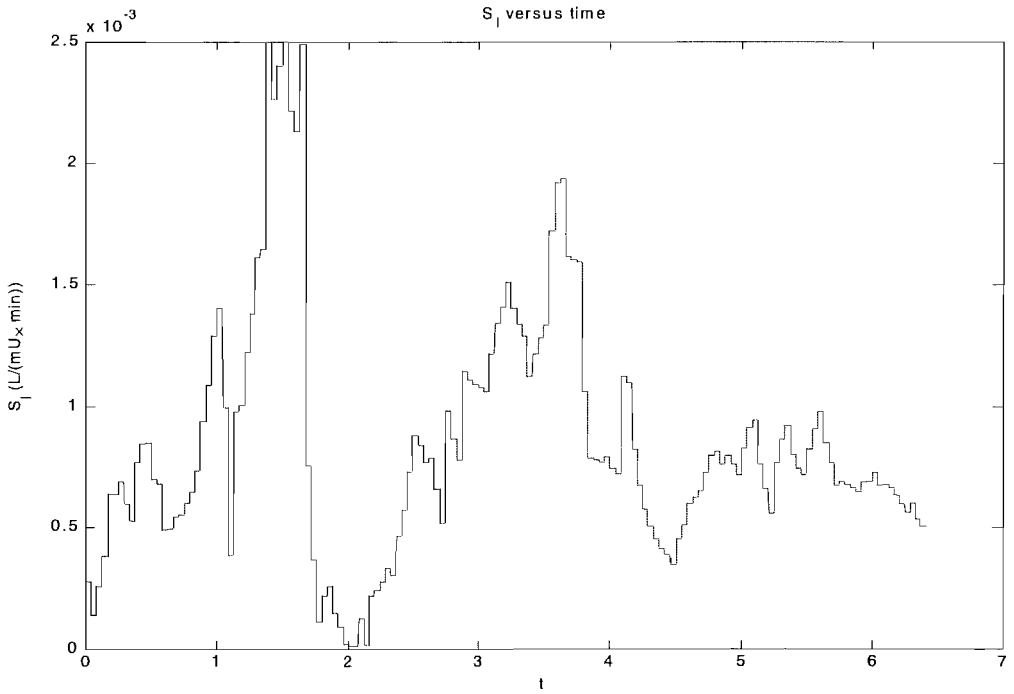


FIGURE 5.2: INSULIN SENSITIVITY VARIATION FROM INITIAL FIT

Using the smoothed patient specific parameters, $p_G$ and $S_I$, the resulting model fit is shown in Figure 5.3. This fit is still well within the error bands created by the data. In addition, the patient specific parameters, $p_G$ and $S_I$, as shown in Figure 5.4 and Figure 5.5 are less noisy and hence more valid.

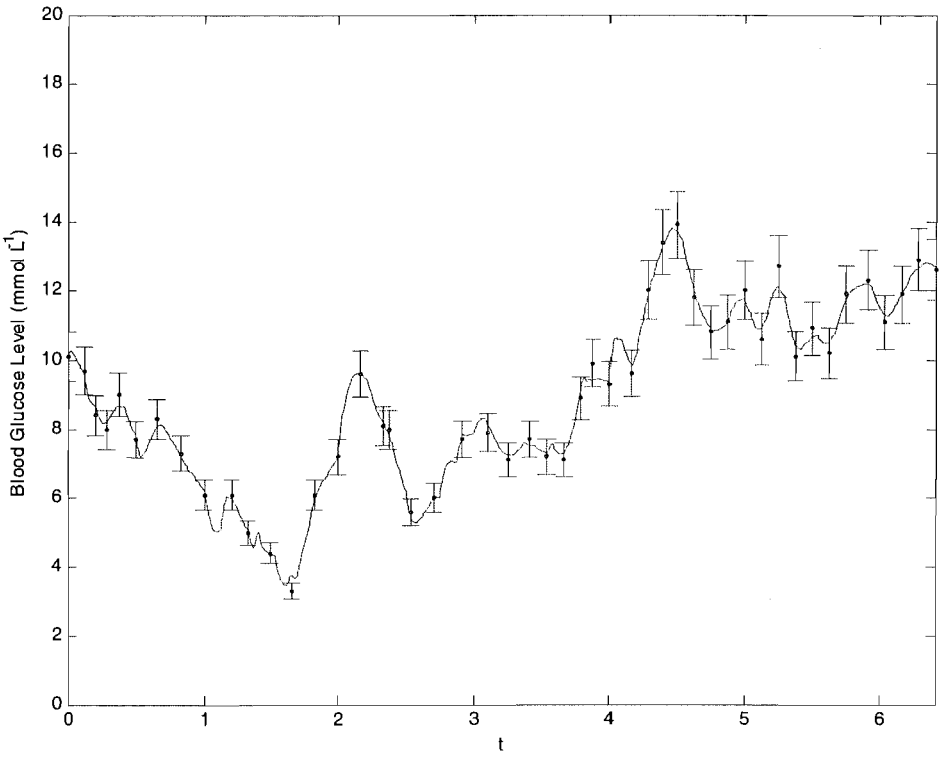


FIGURE 5.3: AN EXAMPLE PATIENT'S BLOOD GLUCOSE DATA AND SMOOTHED FIT

Note that the resulting plot for $p_G$, shown in Figure 5.4, is approximately constant. When the constraints on the model glucose clearance, $p_G$, were relaxed, there was no change in the insulin sensitivity, $S_I$. Also when the magnitude of $p_G$ was changed by changing the constraints, there was no significant change in insulin sensitivity or the overall model fit. Hence, the model is insensitive to variation in glucose clearance, $p_G$, similar to the results reported by McDonald et al (2000).

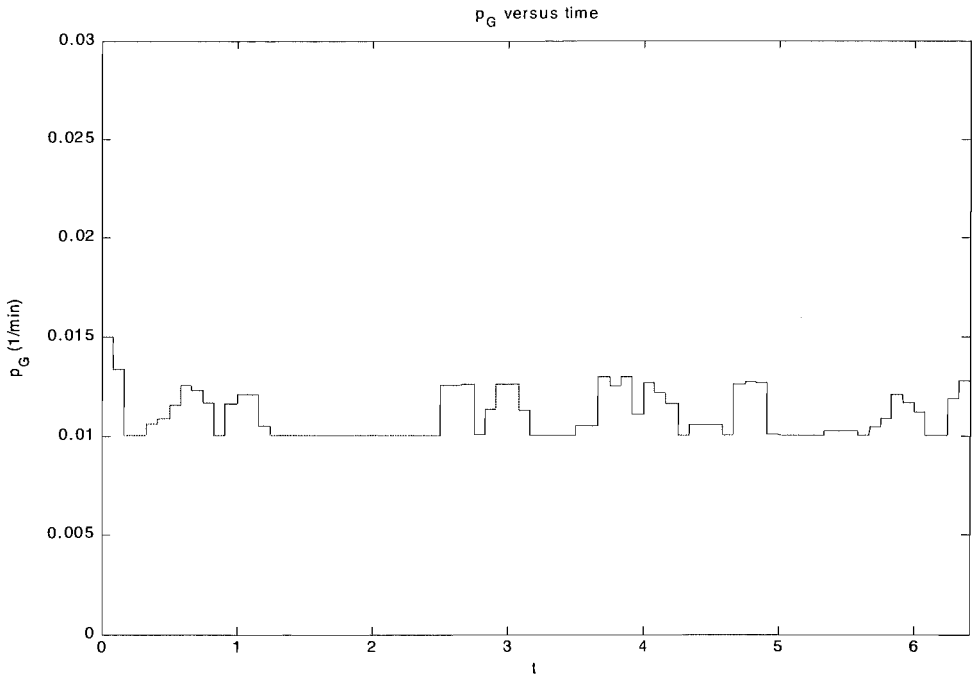


FIGURE 5.4: FRACTIONAL GLUCOSE CLEARANCE FOLLOWING SMOOTHING

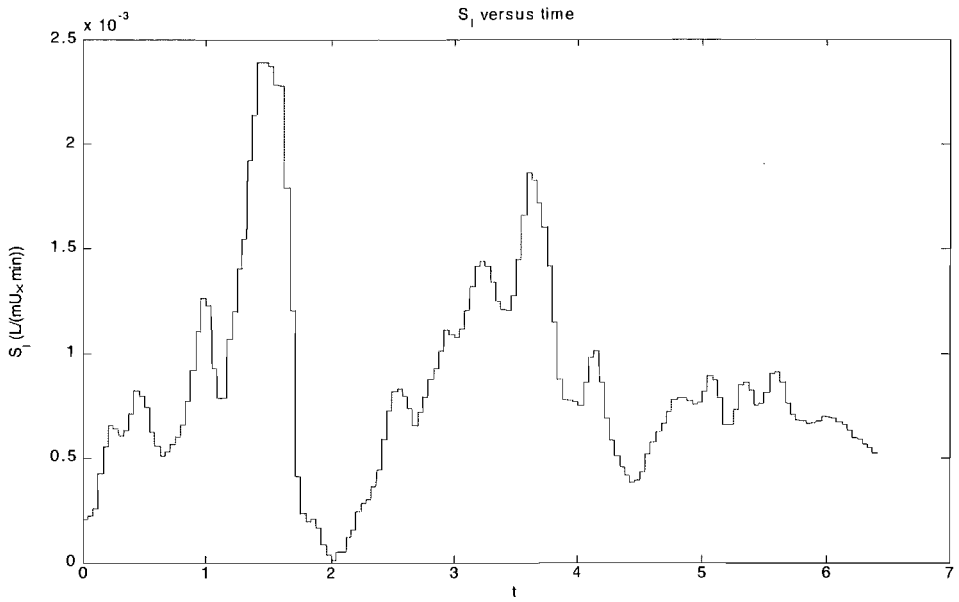


FIGURE 5.5: INSULIN SENSITIVITY FOLLOWING SMOOTHING

The insulin sensitivity, $S_I$, following smoothing, as shown in Figure 5.5 appears to be oscillatory, with periods of approximately two days and smaller oscillations on top of that at approximately 16 - 20 hours. This result shows the possibility of a diurnal variation in this patient. If the insulin sensitivity was held constant, this change in the patient's physiological parameter dynamics may have been missed and resulted in significant model error. The diurnal variation in insulin sensitivity, although thought likely in healthy individuals (Wilinska, et al., 2003), is an idea that has not been considered in much depth in critically ill patients.

## 5.3 SUMMARY

Patient specific parameters require an optimisation or fitting method to assign patient specific values for a patient. More specifically, as both glucose clearance and insulin sensitivity are expected to vary with time, the parameters calculated by the proposed identification technique require physiological verification. Physiological verification in this case, comes from limiting both the range and variation of the optimised values to realistic, reported ranges.

The use of linear regression in the optimisation of patient parameters is numerically simple and hence requires much less computation. It also avoids the problem posed by starting point dependent methods, such as non-linear recursive least squares, where multiple starting points are required. Overall, the use of this parameter identification method gives

excellent fits, as discussed later, which allow metabolic changes to be reflected accurately in patient specific parameters.

## 5.4 REFERENCES

Hovorka, R. and Vicini, P. (2001). Parameter Estimation. In E. Carson and C. Cobelli (Eds.), *Modelling Methodology for Physiology and Medicine.* 107-151. London: Academic Press.

McDonald, C., Dunaif, A. and Finegood, D. T. 2000. Minimal-Model Estimates of Insulin Sensitivity Are Insensitive to Errors in Glucose Effectiveness. *J Clin Endocrinol Metab.* 85(7): 2504-2508

Wilinska, M. E., Chassin, L. J., Schaller, H. C., Pieber, T. R. and Hovorka, R. (2003). Modelling Insulin Lispro Kinetics During Physiological Conditions in Subjects with Type 1 Diabetes Treated by CSII. Proc *World Congress on Biomedical Engineering and Medical Physics* in Sydney, Australia. 24-29 August 2003.

# 6

# TARGETED GLUCOSE REGULATION

## 6.1 INTRODUCTION

To apply the control model developed in a clinical environment, it has to be combined with a sensor and feedback controller. The overall objective is safely reducing elevated blood glucose levels or maintaining an acceptable blood glucose level. Adaptive control is used to monitor the physiological status of a critical care patient, allowing tight glycemic control to be achieved in proof of concept trials. Step-wise targeted reduction of blood glucose levels reduces blood glucose safely and allows the patients progress and metabolic state to be closely monitored.

The proof of concept clinical trials span five hours and begin with an insulin challenge over a one hour period, followed by four hours of tight blood glucose control. Each hour the controller uses bolus injections to achieve a target blood glucose value. Target blood glucose levels are selected 10 – 20% below the current blood glucose levels, with the drop dependent on the extent of the patient's elevated blood glucose level and a minimum target

of 4.5 mmol/L. During the trial, patients are subjected to a constant, nasal-gastric feed of 1000 calories of glucose per day, which is the standard protocol in the Christchurch Hospital ICU. Ethical consent for these trials was obtained from the Canterbury Ethics Committee.

## 6.2 TRIAL PROCEDURE

### *6.2.1 Patient Selection*

The selection criteria are designed to include stable, hyperglycemic patients, but also to test the control algorithm across a range of patients with varying injuries, illnesses and physiological states. Patients had to be older than 16 years with random blood glucose levels greater than 8 mmol/L. They also were required to be on a constant nasal-gastric feed and have an arterial cannula. Exclusion criteria included patients that were not expected to survive 72 hours, patients receiving neuromuscular blockade, or patients with morbid obesity (body mass index greater than 35 $kg/m^2$).

### *6.2.2 Trial Outline*

Between 0700 hours and 1000 hours, the patient's insulin infusion is turned off. A constant nasal-gastric feed of 70 ml/hr (0.0918 mmol/(L·min) assuming a 12 L distribution volume) of Isosource™ is maintained throughout this period and the duration of the trial. Paired blood glucose measurements are taken hourly to determine the patient's equilibrium blood glucose level using a bedside Glucocard™ *Test Strip II* glucose testing kit with an absolute error of 7% (Arkray Inc. 2001). At 1000 hours, the patient receives a 1.5 U insulin challenge bolus via an intravenous cannula using a Graseby™ 3500 syringe pump. Paired blood glucose measurements are taken at 15 minute intervals until 1100 hours.

At 1100 hours, the first estimate for the patient specific parameters, $G_E$, $p_G$ and $S_I$, are made using the data collected in the hour following the insulin challenge. An insulin injection frequency of thirty minutes or one hour is determined by the controller according to the predicted patient blood glucose regulatory system behaviour. Paired blood glucose measurements are taken every 30 minutes, and patient specific parameters are re-evaluated each hour using the prior two hours of data. Following each re-evaluation of patient specific parameters, $p_G$ and $S_I$, the insulin injection bolus size to achieve the sub-target is determined by the controller. Blood glucose level sub-targets are set for 1200, 1300, 1400 and 1500 hours using the prior two hours of data. The goal is a reduction of 10 – 20 % in blood glucose level per hour. The overall approach is therefore a bolus driven adaptive control method that utilises recently obtained data to update the patient specific parameters. The control method is summarised in Figure 6.1.

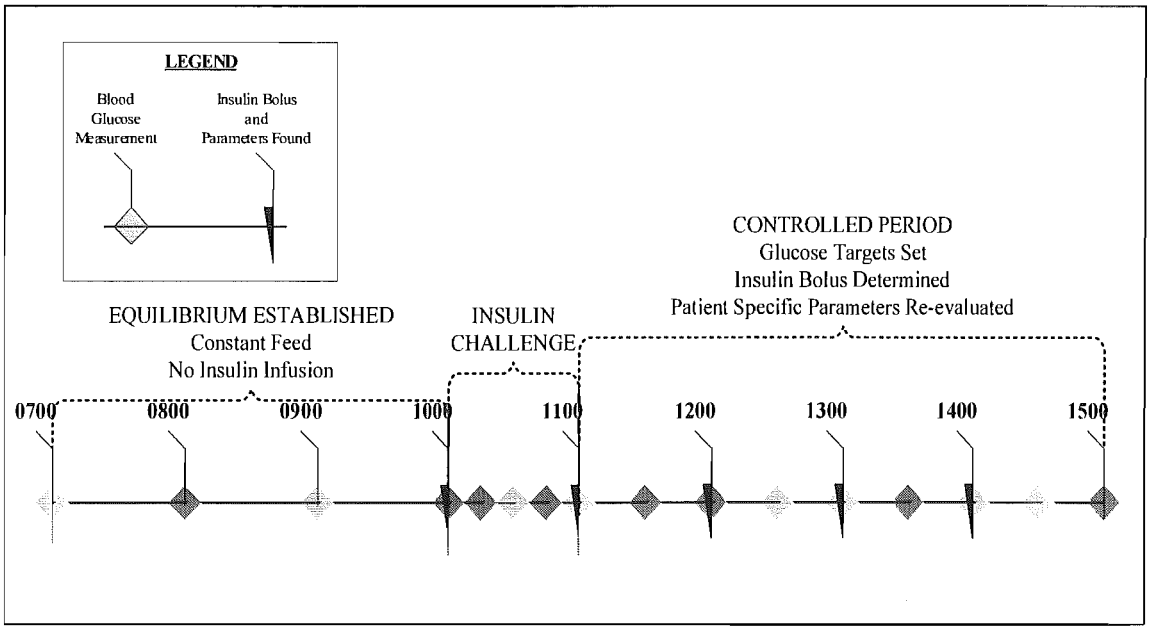


FIGURE 6.1: TIMELINE OF EVENTS DURING CLINICAL TRIAL

To lower a hyperglycemic patient's blood glucose level to a desired target, the identification of patient specific parameters, $p_G$ and $S_I$, is critical. Gradient based optimisation routines have proven difficult due to the infrequent noisy measurements and non-convex parameter dependent problem defined (Chase, et al., 2002; 2003; Doran, et al., 2004a; 2004b). In addition, prior efforts have also shown that these parameters vary over time. By frequently checking and recalculating these values, the controller aims to, first, find accurate parameter values and, second, capture any variation in the patient's metabolic state due to external perturbations to the system.

In model terms, the equilibrium blood glucose level is the value a patient's blood glucose reaches when there are no external inputs. Although critically ill patients have elevated equilibrium glucose levels, determining this level for a patient is difficult, as it requires the patient to be fasted, potentially restricting their ability to fight illness or injury. Fasting also

requires additional effort and monitoring by medical staff. However, a good approximation of the equilibrium glucose level, $G_E$, is important to being able to determine an optimal bolus size. Hence, the basal, or equilibrium, glucose level is assumed to be the same as the 1000 hours blood glucose measurement, which follows three hours of constant feed with no insulin infusion. The assumption is that this level represents a steady state equilibrium value.

Another challenge in determining the optimal insulin bolus is the extent of endogenous insulin production. Endogenous insulin production is often impaired due to both stress of a patient's condition and concurrent drug-therapy. The identification of endogenous insulin production is a relatively complex and time-consuming procedure, often utilising a clamp technique. For the control algorithm presented to find its way into mainstream clinical practice, simplicity is essential. Hence, a value for endogenously produced insulin must be estimated. Past clinical trials, such as those by Hovorka et al (2002), have not required estimations of endogenous insulin as they focus on Type 1 diabetic individuals who are unable to produce insulin. These trials initially assume that the majority of endogenous insulin production is suppressed by the exogenous insulin infusions.

Patient specific parameters, $p_G$ and $S_I$, are identified before each insulin infusion bolus, using the past two hours of data. Fitting less than two hours of data would be inadequate as not enough data would be available. A period longer than two hours would potentially miss dynamics such as the variations described by Wilinska et al (2003). More

importantly, variations due to insulin inhibiting or enhancing drug-therapy might also be excluded.

The effective half-life of insulin in the plasma, $k$, is defined as a generic parameter, but the current model gives the opportunity to change the half-life, at any hour. Insulin sensitivity, $S_I$, should be roughly constant over a five hour period, with changes occurring gradually. If the plot of insulin sensitivity, $S_I$, is taking on a saw-tooth profile, it indicates that the half-life may be incorrect. By decreasing the half-life, and hence increasing $k$, the time immediately following the insulin bolus is accentuated, and the insulin sensitivity, does not have to vary linearly over each hour to compensate for the differences between insulin availability in the model and the patient.

The trials conducted show the progression of the model and controller. The first four trials use the model based on that developed by Doran et al (2004a; 2004b), as shown in Equations (3.5) and (3.6). The following two trials use the model that includes both insulin appearance and glucose clearance saturation, as shown in Equations (3.21) – (3.23). The clinical trials verify the need for these new saturation dynamics, and the data from the first four trials can be used to rerun trials virtually, further verifying the model dynamics.

## 6.3 RESULTS AND DISCUSSION FROM CLINICAL TRIALS

### *6.3.1 Unsaturated Trials*

The first two clinical trials were undertaken to verify the glucose kinetics in the model in Equations (3.5) and (3.6). Hence, saturation effects were not included and the model employed is defined:

$$\dot{G} = -p_G G - S_I (G + G_E) k \int_0^t I(\tau) e^{-k(t-\tau)} d\tau + P(t) \tag{6.1}$$

$$\dot{I} = -n(I + I_B) + \frac{u(t)}{V_I} \tag{6.2}$$

where:

$G$ = concentration of the plasma glucose above the basal level (mmol/L)

$G_E$ = equilibrium level for plasma glucose concentration (mmol/L)

$I$ = concentration of the plasma insulin above basal level (mU/L)

$I_B$ = basal level for plasma insulin concentration (mU/L)

$P(t)$ = exogenous glucose infusion rate (mmol/(L·min))

$u(t)$ = insulin infusion rate (mU /min)

$V_I$ = assumed insulin distribution volume (L)

$p_G$ = fractional clearance of glucose at basal insulin ($min^{-1}$)

$S_I$ = insulin sensitivity (L/(mU·min))

$n$ = first order decay rate constant for insulin in plasma ($min^{-1}$)

$k$ = parameter controlling the half life of insulin ($min^{-1}$)

The insulin infusion equation includes endogenously produced insulin, $U_0 = nV_I I_B$, as well as exogenously infused insulin, $u(t)$. For these trials, critically ill patients were assumed to have their endogenous insulin production suppressed by the elevated counter-regulatory hormones present (Rizza, et al., 1981). The effective half life of insulin, $k$, is set to 70 minutes based upon the 50 - 120 minute range given for sub-cutaneous insulin in Kraegen and Chisholm (1984) and Turnheim and Waldhausl (1988), as discussed in Chapter 4. The generic variable values used in these trials are shown in Table 6.1.

TABLE 6.1: GENERIC PARAMETERS USED IN TRIAL 1 AND 2

| Parameter | Value |
|---|---|
| $I_B$ | 15 mU/L |
| $P(t)$ | 0.0918 mmol/(L·min) |
| $U_0$ | 16.7 mU/min |
| $V_I$ | 12 L |
| $n$ | 0.093 $min^{-1}$ |
| $k$ | 0.0099 $min^{-1}$ |

The results from the first two trials showed that improvements needed to be made. The assumption of suppressed endogenous insulin production was shown to be inaccurate. Figure 6.2 and Figure 6.3 show the comparison between the original endogenous insulin assumption and post-trial analysis where all endogenous insulin was assumed to be present. This change dramatically improved the model fit to the measured data. Note that the sudden jump in Figure 6.3 is due to a 10g glucose IV infusion to treat a hypoglycemic episode.

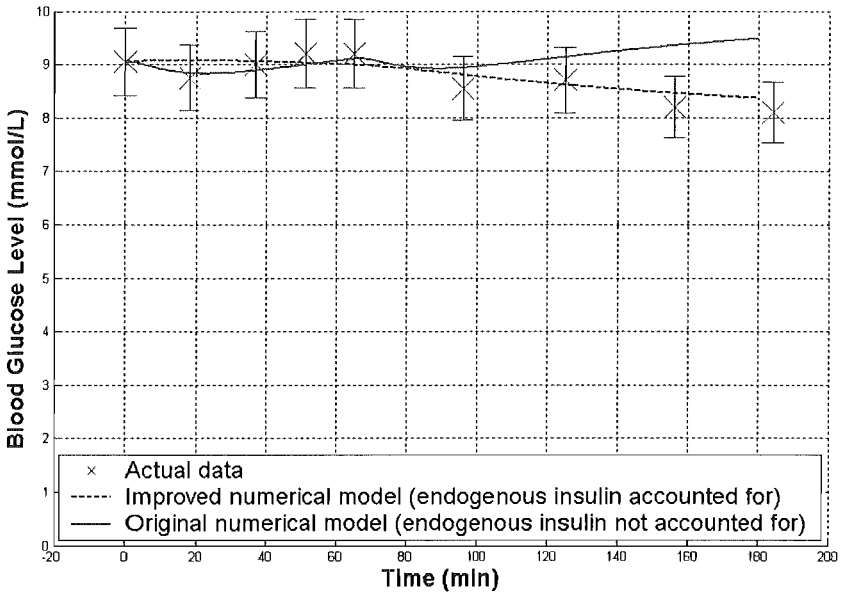


FIGURE 6.2: TRIAL 1 RESULTS SHOWING BOTH INITIAL ASSUMPTION OF NO EXOGENOUS INSULIN, AND POST-TRIAL ANALYSIS WHICH INCLUDES ENDOGENOUS INSULIN

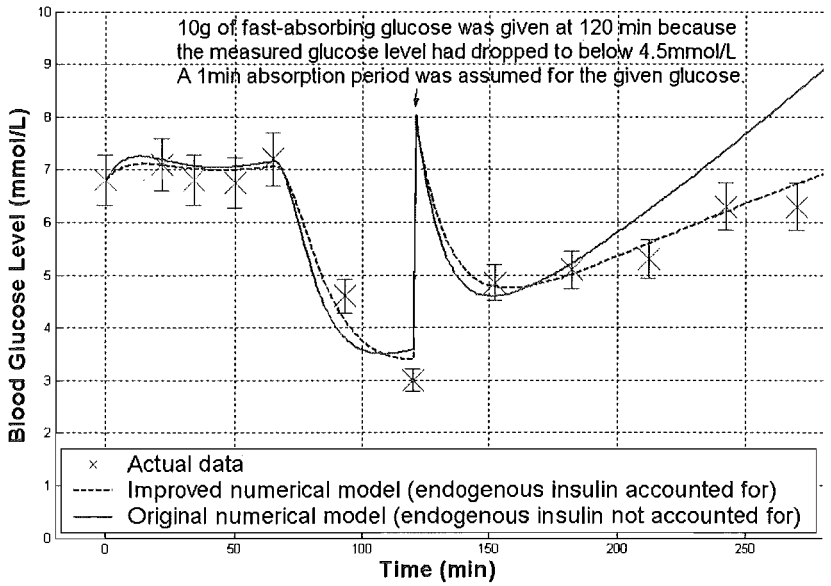


FIGURE 6.3: TRIAL 2 RESULTS SHOWING BOTH INITIAL ASSUMPTION OF NO EXOGENOUS INSULIN, AND POST-TRIAL ANALYSIS WHICH INCLUDES ENDOGENOUS INSULIN

### *6.3.2 Improved Unsaturated Model Trials*

The next two trials used the same control model as trials 1 and 2, but no infusion was made to account for suppressed endogenous insulin , as was done in the first two trials. The number of parameters determined by optimisation was also increased. Both the equilibrium glucose level, $G_E$, and the endogenous insulin production, $U_0$, were optimised hourly, along with the patient specific parameters from the first trial, $p_G$ and $S_I$. There was also scope to change the assumed value of the plasma insulin basal level, $I_B$, if the fit was not ideal, followed by refitting the equilibrium glucose level, $G_E$, and the endogenous insulin production, $U_0$. The remaining generic parameters are shown in Table 6.1.

*Trial 3*

Patient 3 was a 62 year old male suffering from pneumonia, and the trial was completed on the fifth day of the patient's stay. The patient's initial glucose value was 8.5 mmol/L, however the optimisation procedure found an equilibrium glucose value, $G_E$, of 7.5 mmol/L. As both the initial and equilibrium glucose values showed only moderate hyperglycemia, the sub-targets were designed to reduce blood glucose by 10% each hour. This patient was found to have a very low level of endogenous insulin production, as shown by a $U_0$ value of 0.0008 mU/min. The measured glucose data, model simulation and insulin infusion values for trial three are shown in Figure 6.4. The circle marked data indicates a target set the hour previously and a point the model predicted it would hit at that time.

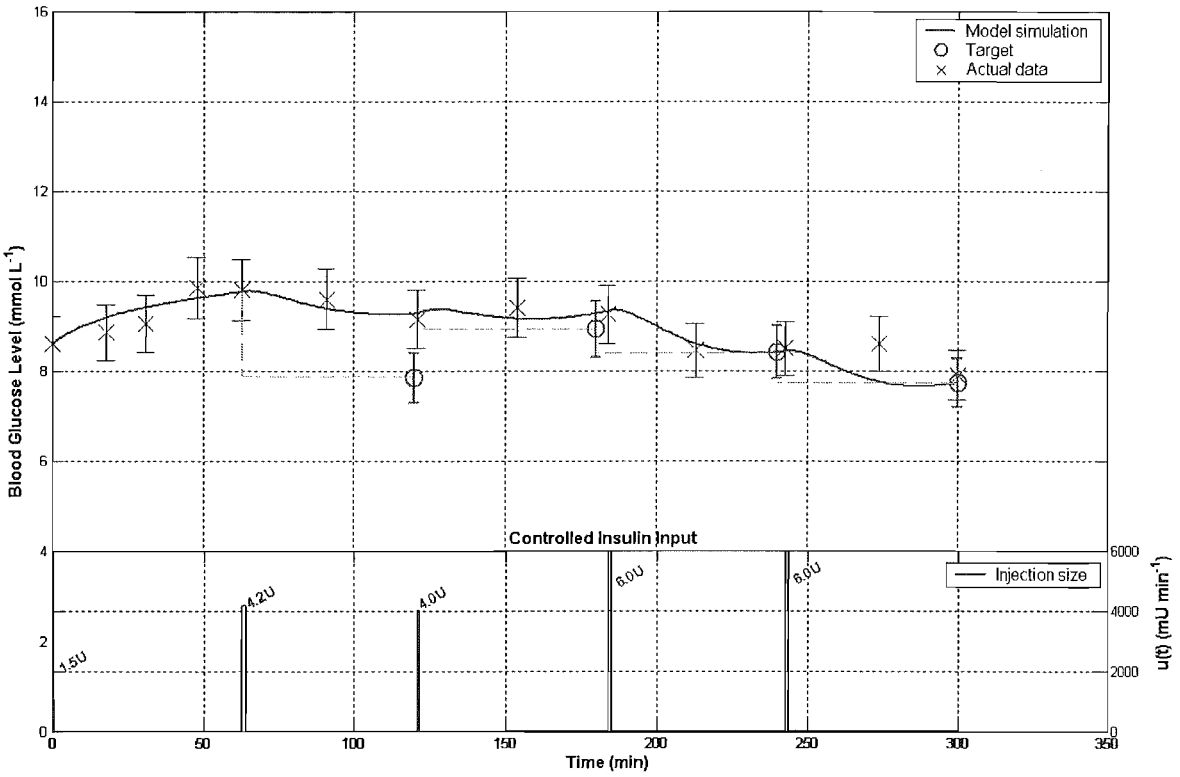


FIGURE 6.4: TRIAL 3 RESULTS SHOWING GLUCOSE DATA AND MODEL SIMULATION AND INSULIN INFUSION VALUES

The results of the third trial showed the patient to be highly insulin resistant, as shown by the low insulin sensitivity value fitted and shown in Figure 6.5. Therefore, significant insulin infusion boluses were required to reduce blood glucose levels, as shown in Figure 6.4. It should be noted that although, an insulin bolus of 6 U may seem extremely large, these patients are also on a constant feed. For safety during these proof of concept trials, the recommended insulin infusion is displayed and then manually infused, placing a human check in the control loop. When the injection size determined by the controller exceeds 6 U, a saturation of 4 U and then 6 U is enforced, ensuring patient safety by safeguarding against hypoglycemic episodes. This procedure was required for trial three, as shown in

Figure 6.4, with the 4 U insulin bolus saturation put in place at 120 minutes, and the 6 U insulin bolus saturation in place at 180 and 240 minute infusions. In this case, the 4 U saturation resulted in the measured glucose being slightly higher than the desired target, though still within the error bands. However, the 6 U saturation allowed the controller to reach its targets, strongly suggesting the presence of metabolic saturation at these levels of insulin infusions.

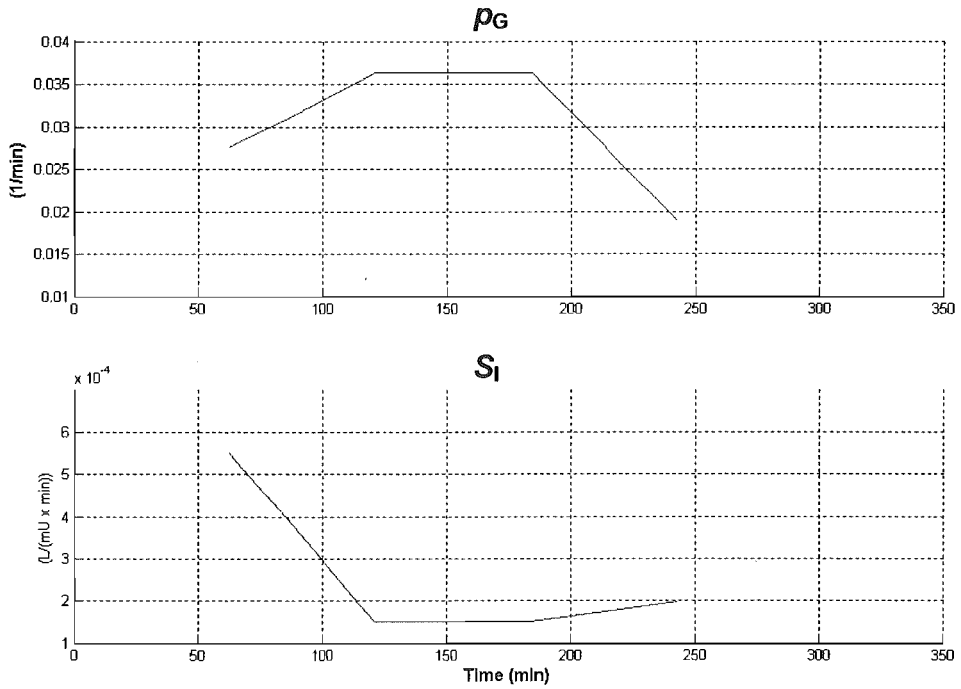


FIGURE 6.5: VARIATIONS IN PATIENT SPECIFIC PARAMETERS FOR TRIAL 3

The advantage of the re-evaluation and recalculation used in the controller is shown in Figure 6.4 and Table 6.2, as the targets were reached more accurately as the trial progressed. After 120 minutes, the controller had captured the high insulin resistance found in this patient, as seen in Figure 6.5, and insulin boluses following this were more effective, as shown in Figure 6.4. Further injections might have shown greater effect on lowing blood glucose if the trial was continued past its five hour period.

TABLE 6.2: COMPARISON BETWEEN TARGET AND ACHIEVED GLUCOSE LEVELS FOR TRIAL 3

| Time (min) | Target Glucose (mmol/L) | Achieved Glucose (mmol/L) | Error %(abs) |
|---|---|---|---|
| 120 | 7.84 | 9.15 | 17 % (1.31) |
| 180 | 8.92 | 9.25 | 4 % (0.33) |
| 240 | 8.40 | 8.50 | 1 % (0.10) |
| 300 | 7.73 | 7.90 | 2 % (0.17) |

*Trial 4*

Patient 4 was a 71 year old male with a subarachnoid haemorrhage and secondary aspiration pneumonia, in his fourth day in the ICU. The initial blood glucose level of 13.4 mmol/L is high, but not uncommon in ICU settings, and the equilibrium blood glucose level, $G_E$, was found to be 12.88 mmol/L. Sub-targets were assigned to reduce blood glucose by 20% per hour. Unlike the patient in the third trial, this patient was found to have a relatively high level of endogenously produced insulin, $U_0$ = 56.56 mU/min, which is over three times higher than normal (Bergman, et al., 1985; Furler, et al., 1985). The

measured glucose data, model simulation and insulin infusion values for trial three are shown in Figure 6.6.

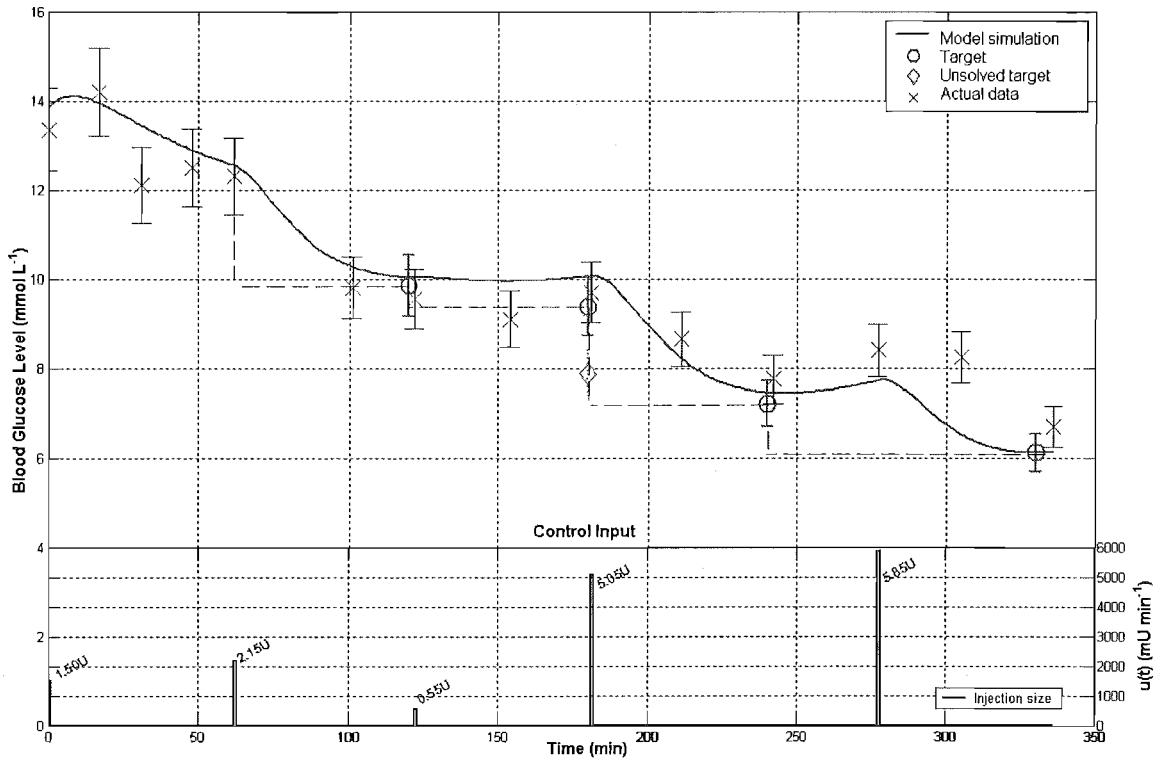


FIGURE 6.6: TRIAL 4 RESULTS SHOWING GLUCOSE DATA AND MODEL SIMULATION AND INSULIN INFUSION VALUES

Very good approximations of the patient specific parameters, $p_G$ and $S_I$, were obtained immediately after the 60 minute insulin challenge period, as shown by the consistency in $p_G$ and $S_I$ over the following 120 minutes in Figure 6.7. At the end of the 120 minutes, an insulin bolus solution could not be found to achieve the intended target of 7.9 mmol/L at 180 minutes, as shown by the diamond mark in Figure 6.6. The failure to find a solution for the insulin bolus led to the use of a standard 0.55 U bolus and re-adjustment of the target value to 9.3 mmol/L. By setting a less difficult target, solutions for the patient

specific parameters were obtained, and additional data was gathered to assist in the bolus calculation to meet the target at 240 minutes. The inability of the program to find physiologically valid, patient specific values indicated the need for the improved identification algorithms discussed in Chapter 5.

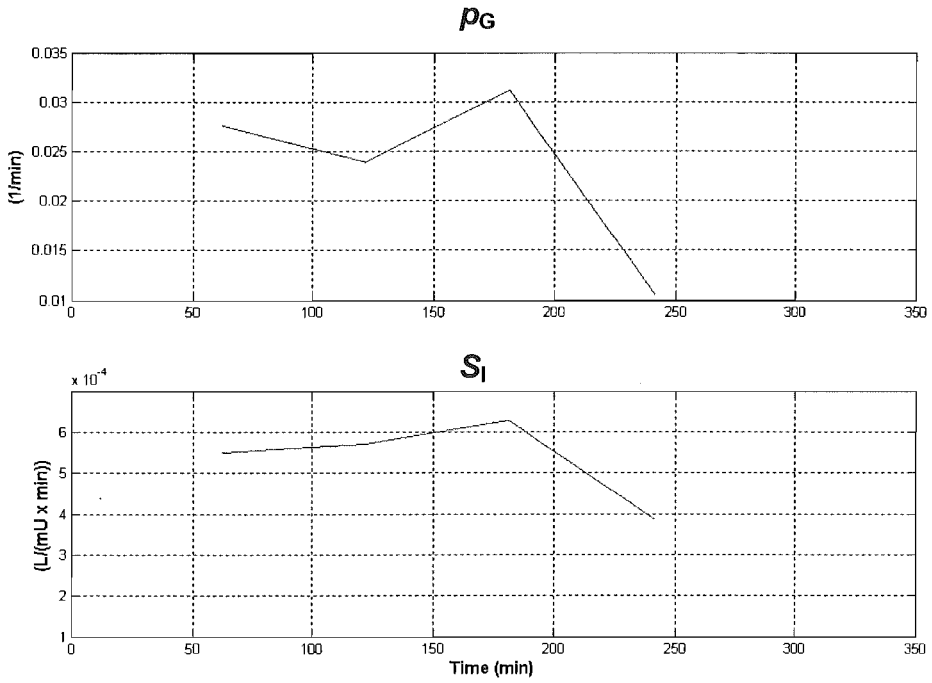


FIGURE 6.7: VARIATIONS IN PATIENT SPECIFIC PARAMETERS FOR TRIAL 4

After the trial, a potential cause of the non-convergence at 240 minutes displayed in Figure 6.6 was found. The patient was given Metoprolol™, a β-blocker that enhances the effect of insulin, at approximately 120 minutes into the trial. Metoprolol™ is a fast acting drug with an effective life of 2 to 3 hours (Cruickshank and Prichard, 1994). At 240 minutes into the trial, it is thought that the effect of the Metoprolol™ was diminishing, as reflected by the controller identifying a reduction in both $p_G$ and $S_I$ at 240 minutes in Figure 6.7. In

addition, the errors in Table 6.3 increased at this time while the adaptive control model began to adjust to this sudden externally induced change in behaviour.

TABLE 6.3: COMPARISON BETWEEN TARGET AND ACHIEVED GLUCOSE LEVELS FOR TRIAL 4

| Time (min) | Target Glucose (mmol/L) | Achieved Glucose (mmol/L) | Error % (abs) |
|---|---|---|---|
| 120 | 9.55 | 9.10 | 5 % (-0.45) |
| 180 | 9.70 | 9.40 | 3 % (-0.30) |
| 240 | 7.20 | 7.75 | 8 % (0.55) |
| 300 | 6.70 | 6.12 | 9 % (-0.58) |

The desired stepwise reduction in blood glucose is clearly seen in the fourth trial, reducing the patient's blood glucose level from 13.4 mmol/L to 6.7 mmol/L over four hours, in four succinct steps. The responsive nature of the controller was shown to be advantageous in a clinical environment where patients are often subjected to external perturbations, such as drug therapy, which may affect their metabolic response to insulin doses. Changes in the metabolic response due to drug therapy in critically ill patients can also be likened to metabolic changes in ambulatory diabetic individuals during or after exercise (e.g. (Derouich and Boutayeb, 2002; Duncan, et al., 2003), illustrating the advantages of adaptive control in both a clinical environment and potentially in day to day life.

### *6.3.3 Verifying the Addition of Saturation*

The data gathered from Trials 3 and 4 was used to verify the addition of glucose clearance and insulin saturation to the model. The literature survey completed for Chapter 4 showed merit in the use of these two saturation modes, but before it could be used in clinical trials the new saturation model needed to be tested in simulation. By adding saturation, the amount of insulin utilised by the body could be compared to the amount infused. The goal is to ensure the controller uses insulin more efficiently and does not allow insulin to accumulate.

The results presented show the same measured blood glucose data, blood glucose targets and insulin bolus sizes as in Figure 6.4 and Figure 6.6. The difference is the model used and the method in Chapter 5 was used to find patient specific parameters, $p_G$ and $S_I$. Both trials were re-evaluated using the parameters in Table 6.4.

TABLE 6.4: GENERIC PARAMETERS USED FOR RERUNNING THE MODEL IN TRIALS 3 AND 4

| Parameter | Value |
|---|---|
| $P(t)$ | 0.0918 mmol/(L·min) |
| $V_I$ | 12 L |
| $n$ | 0.16 $min^{-1}$ |
| $k$ | 0.0099 $min^{-1}$ |
| $\alpha_G$ | 0.015 |
| $\alpha_I$ | $1.7 \times 10^{-3}$ |

*Trial 3 Re-evaluated with Saturation Model*

The effect of the saturation in the model can be seen by comparing the original model output in Figure 6.4 to the saturated model output in Figure 6.9. The saturated model output captures each of the measured blood glucose points with greater accuracy. This increased accuracy is especially apparent in the final hour of the trial, where the saturation model captures the glucose rise between 240 and 300 minutes.

The effect of saturation on delayed insulin in the blood is shown in Figure 6.8, where the area between the two lines represents the insulin unable to be utilised due to saturation. By adding saturation, future trials will not infuse insulin that cannot be utilised, hence decreasing insulin infused for the same metabolic reaction. Saturation also decreases the fitted parameter values as seen in Figure 6.10 where the glucose clearance, $p_G$, ranges from $1.996 \times 10^{-2}$ to $2.017 \times 10^{-2}$ $min^{-1}$ and the insulin sensitivity, $S_I$, ranges from $2.337 \times 10^{-4}$ – $14.619 \times 10^{-4}$ L/(mU·min). Hence, the patient specific values should be a better representation of the actual values.

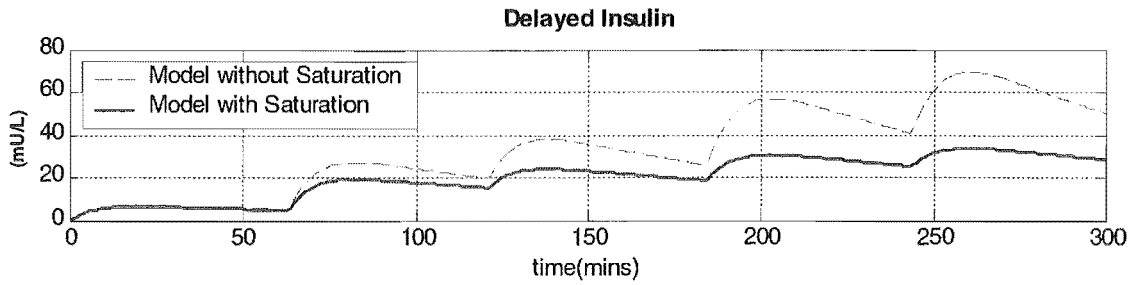


FIGURE 6.8: DELAYED INSULIN IN TRIAL 3 SHOWING THE EFFECT OF SATURATION

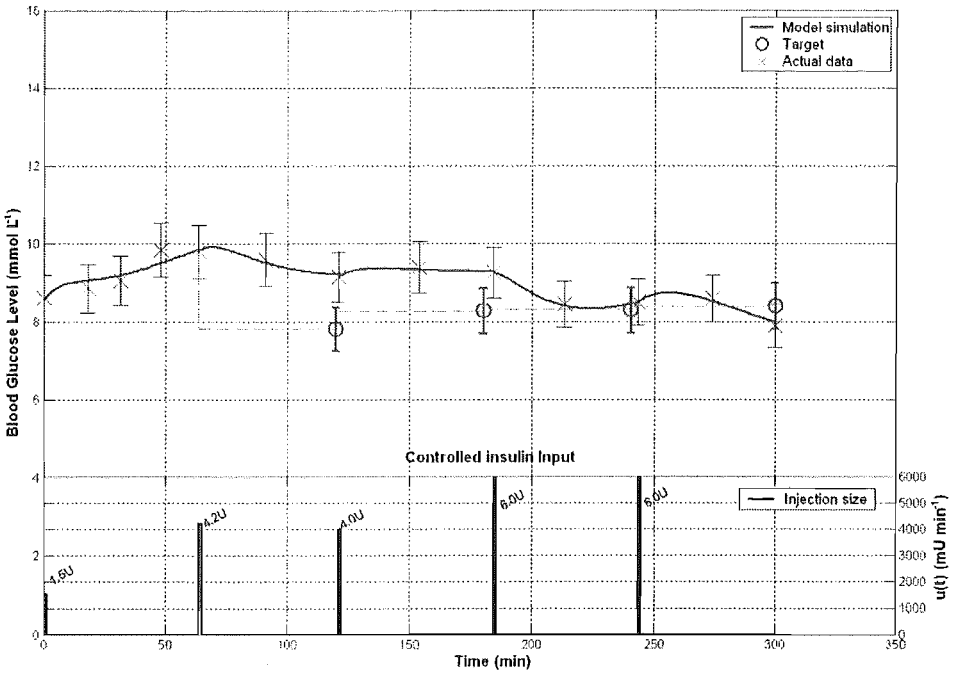


FIGURE 6.9: TRIAL 3 RESULTS SHOWING GLUCOSE DATA AND MODEL SIMULATION WITH THE ADDITION ON SATURATION AND INSULIN INFUSION VALUES

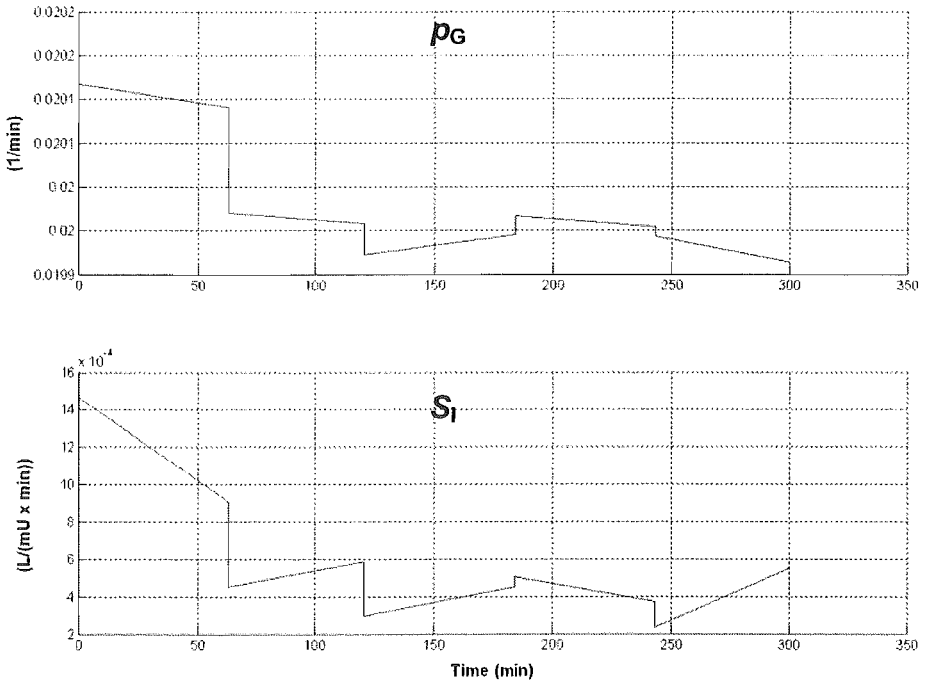


FIGURE 6.10: VARIATIONS IN PATIENT SPECIFIC PARAMETERS AFTER SATURATION IS ADDED TO THE MODEL FOR TRIAL 3

*Trial 4 Re-evaluated with Saturation Model*

The effect of the saturation in the model in trial 4 can be seen by comparing the original model output in Figure 6.6 to the saturation model output in Figure 6.12. The saturation model was much more effective at capturing the measured glucose data points, and once again, patient specific parameters were reduced, as shown in Figure 6.13, where the glucose clearance, $p_G$, ranges from $1.694 \times 10^{-2}$ to $1.990 \times 10^{-2}$ $min^{-1}$ and the insulin sensitivity, $S_I$, ranges from $9.167 \times 10^{-4}$ to $21.466 \times 10^{-4}$ L/(mU·min). The effect of saturation on delayed insulin in the blood is shown in Figure 6.11. As can be seen in Figure 6.8 and Figure 6.11, as the delayed insulin increases in magnitude, the proportion of insulin that is not utilised increases dramatically.

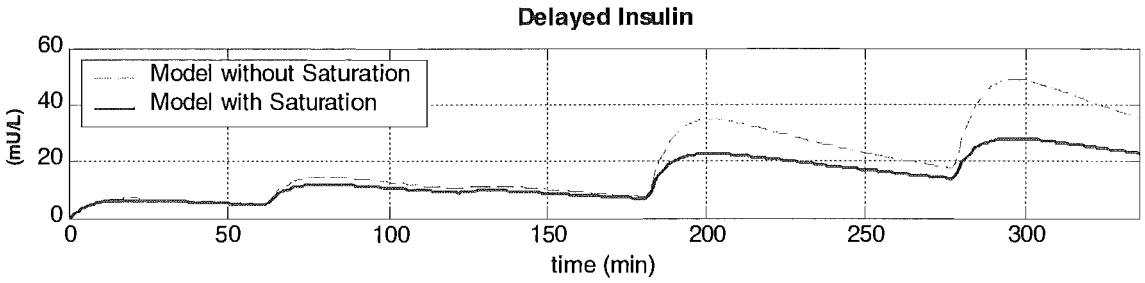


FIGURE 6.11: DELAYED INSULIN IN TRIAL 4 SHOWING THE EFFECT OF SATURATION

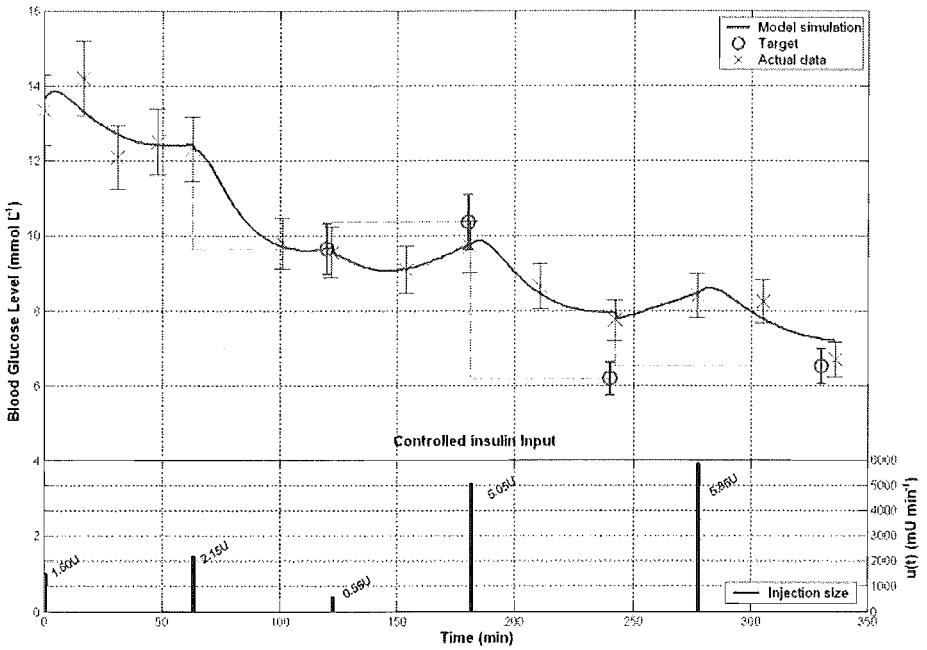


FIGURE 6.12: TRIAL 4 RESULTS SHOWING GLUCOSE DATA AND MODEL SIMULATION WITH THE ADDITION ON SATURATION AND INSULIN INFUSION VALUES

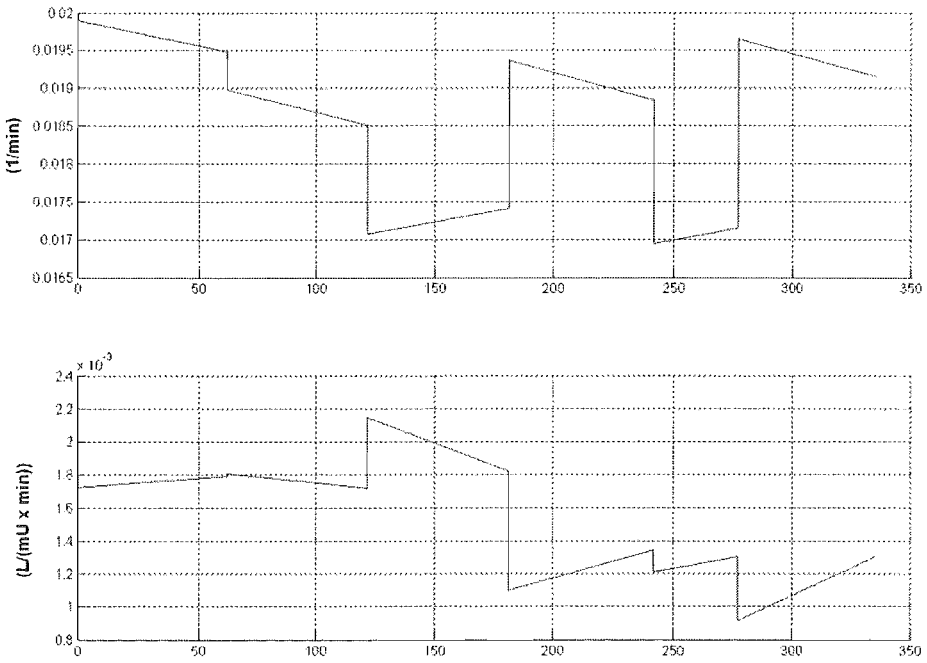


FIGURE 6.13: VARIATIONS IN PATIENT SPECIFIC PARAMETERS AFTER SATURATION IS ADDED TO THE MODEL FOR TRIAL 4

### *6.3.4 Saturated Model Trials*

The final clinical trials were undertaken using the saturated model developed in Chapter 3, which is presented here for review.

$$\dot{G} = -p_G G - S_I (G + G_E)\frac{Q}{1+\alpha_G Q} + P(t) \tag{6.3}$$

$$\dot{Q} = -kQ + kI \tag{6.4}$$

$$\dot{I} = -\frac{nI}{1+\alpha_I I} + {u(t)}/{V_I} \tag{6.5}$$

The main differences between this model and the model used in previous clinical trials are the addition of saturation on insulin appearance and glucose clearance, and the removal of endogenous insulin production. The values for generic parameters used in the fifth trial are shown in Table 6.5. The glucose equilibrium value, $G_E$, is assumed to be the average of the paired blood glucose samples at 1000 hours, for simplicity. New procedures for determining patient specific parameters, $p_G$ and $S_I$, as described in Chapter 5, were also utilised, reducing computation time and giving more optimal values for the parameters.

TABLE 6.5: GENERIC PARAMETERS USED IN TRIAL 5 AND 6

| Parameter | Value |
|---|---|
| $P(t)$ | 0.0918 mmol/(L·min) |
| $V_I$ | 12 L |
| $n$ | 0.16 $min^{-1}$ |
| $k$ | 0.0099 $min^{-1}$ |
| $\alpha_G$ | 0.04 → 0.015 |
| $\alpha_I$ | $1.7 \times 10^{-3}$ |

*Trial 5*

Patient was a 76 year old male in the ICU as a result of respiratory failure secondary to mediastinal sepsis, heart failure and post coronary artery bypass surgery. The patient had spent approximately three months in and out of the ICU following cardiac surgery in December 2003, but when the trial was undertaken, he had been in the ICU for 33 days. The equilibrium glucose level showed only moderate hyperglycemia, and blood glucose levels were targeted to drop only 10% per hour. The measured glucose data, model simulation, insulin infusion values and remaining insulin in the plasma for trial five are shown in Figure 6.14 shows the patient specific parameters found during the trial.

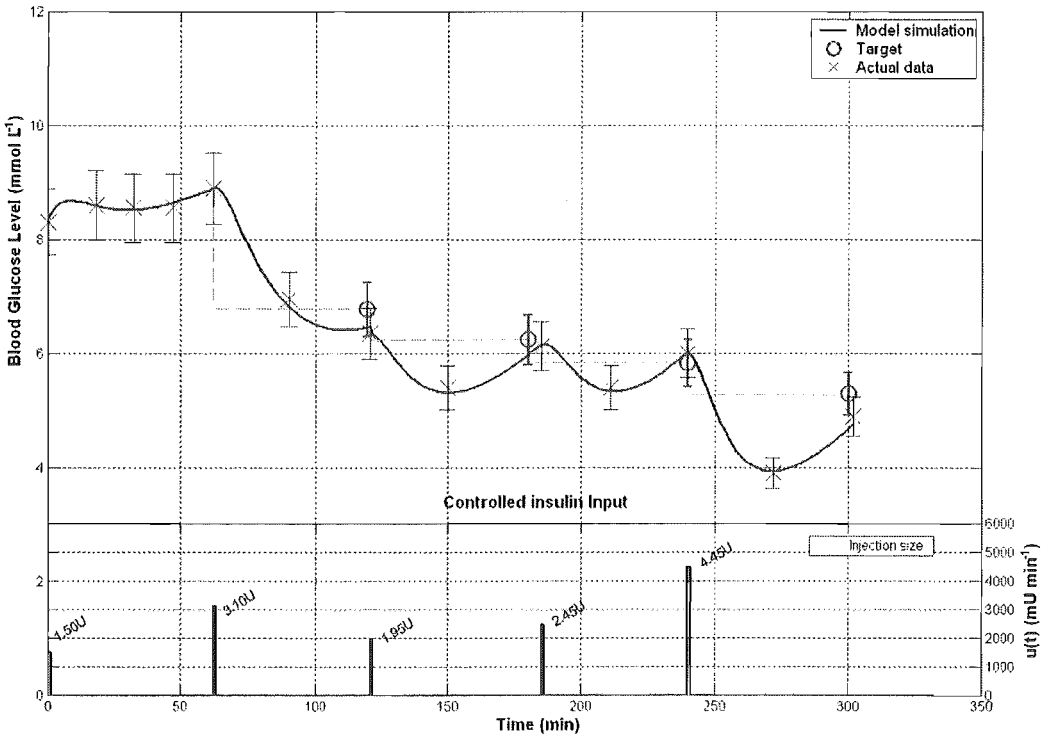


FIGURE 6.14: TRIAL 5 RESULTS SHOWING GLUCOSE DATA, MODEL SIMULATION, AND INSULIN INFUSION VALUES

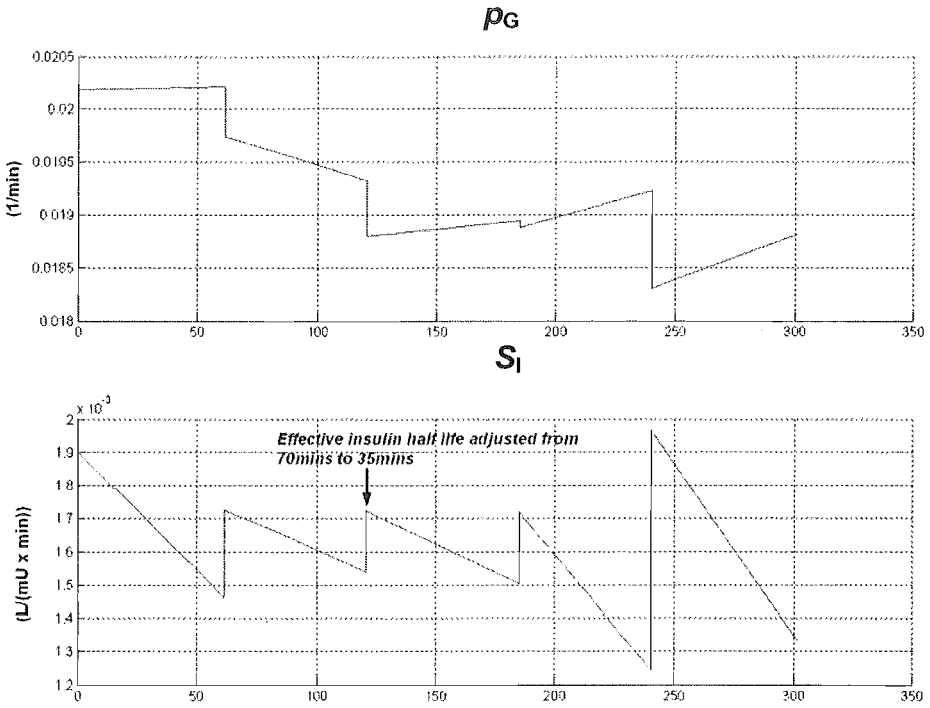


FIGURE 6.15: VARIATIONS IN PATIENT SPECIFIC PARAMETERS FOR TRIAL 5

The new model correlated very well with measured glucose data. Table 6.6 shows the accuracy with which target levels were achieved. The average error is 4.25 %, which is within the measurement error.

TABLE 6.6: COMPARISON BETWEEN TARGET AND ACHIEVED GLUCOSE LEVELS FOR TRIAL 5

| Time (min) | Target Glucose (mmol/L) | Achieved Glucose (mmol/L) | Error %(abs) |
|---|---|---|---|
| 120 | 6.78 | 6.35 | 6 % (-0.43) |
| 180 | 6.23 | 6.13 | 2 % (-0.10) |
| 240 | 5.70 | 6.00 | 5 % (-0.30) |
| 300 | 5.20 | 4.90 | 6 % (-0.30) |

The inability of the model to capture the dip in blood glucose levels between 240 and 300 minutes is interesting. The insulin bolus prescribed by the controller was lower than it would have been in the model used in the first four trials as it accounted for the effect of saturation on glucose clearance. In post-trial analysis, the effect of lowering the saturation on glucose clearance by reducing the parameter $a_G$ from 0.04 to 0.015, as used by Natali et al (2000), allowed the model to more closely follow the blood glucose measurements between 240 and 300 minutes, without compromising the fits leading up to this period.

Throughout this trial, insulin sensitivity, $S_I$, took on a saw-tooth shape, as seen in Figure 6.15. An explanation for the saw-tooth shape shown is that the half-life for insulin disappearance, defined by $k$, was too long. When the half-life is reduced, insulin in the model is cleared more quickly, and the insulin sensitivity parameter, $S_I$, fitted did not have to compensate. When the insulin disappearance parameter, $k$, was doubled or tripled (reducing the half-life from 70 to 35 minutes or 23 minutes), the saw-tooth shape and large variance was lost. Given that the glucose clearance, $p_G$, was still virtually constant, this result also highlights the relative independence and insensitivity of the glucose clearance parameter, $p_G$, to changes in insulin sensitivity, $S_I$, in this model

As an example, Figure 6.16 shows the effect of tripling $k$, and reducing $a_G$ from 0.04 to 0.015. Note how the dip between 240 and 300 minutes is captured more effectively, as a result of the decreased half-life and reduced impact of glucose clearance saturation. The variation in insulin sensitivity has also been reduced. Post-trial analysis showed that an even better fit and lowered insulin sensitivity ($1.30 \times 10^{-3}$ - $1.90 \times 10^{-3}$ L/(mU·min)) was

found with no saturation on glucose clearance and a half-life of 35 minutes, suggesting this patient was not achieving a level of insulin high enough to induce glucose clearance saturation in their system.

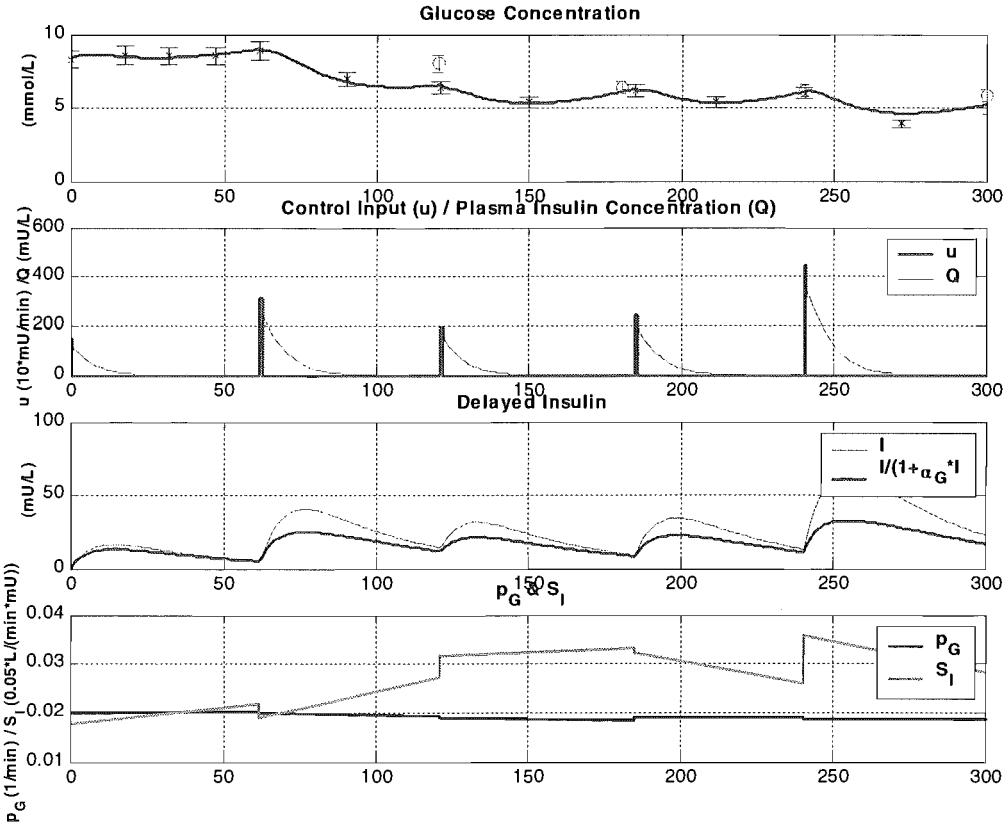


FIGURE 6.16: TRIAL 5 RESULTS SHOWING GLUCOSE DATA, MODEL SIMULATION, INSULIN INFUSION VALUES AND REMAINING INSULIN IN THE PLASMA WITH REDUCED HALF-LIFE AND GLUCOSE CLEARANCE SATURATION

*Trial 6*

Patient 6 was a 77 year old female suffering from sepsis, and the trial was completed on the 30th day of the patient's stay. The equilibrium glucose level showed only moderate hyperglycemia, and blood glucose levels were targeted to drop by 15 % per hour. The measured glucose data, model simulation, insulin infusion values and remaining insulin in the plasma for trial six are shown in Figure 6.17. Figure 6.18 shows the patient specific parameters found during the trial.

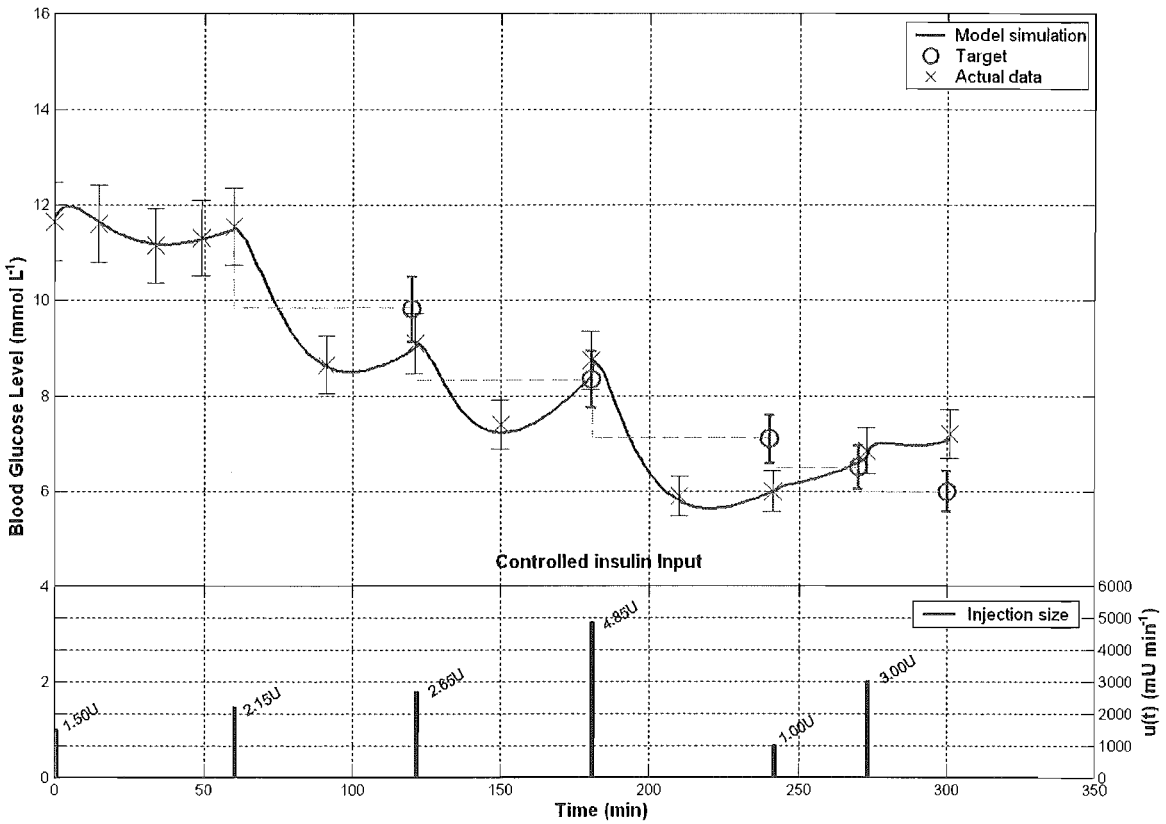


FIGURE 6.17: TRIAL 6 RESULTS SHOWING GLUCOSE DATA, MODEL SIMULATION, AND INSULIN INFUSION VALUES

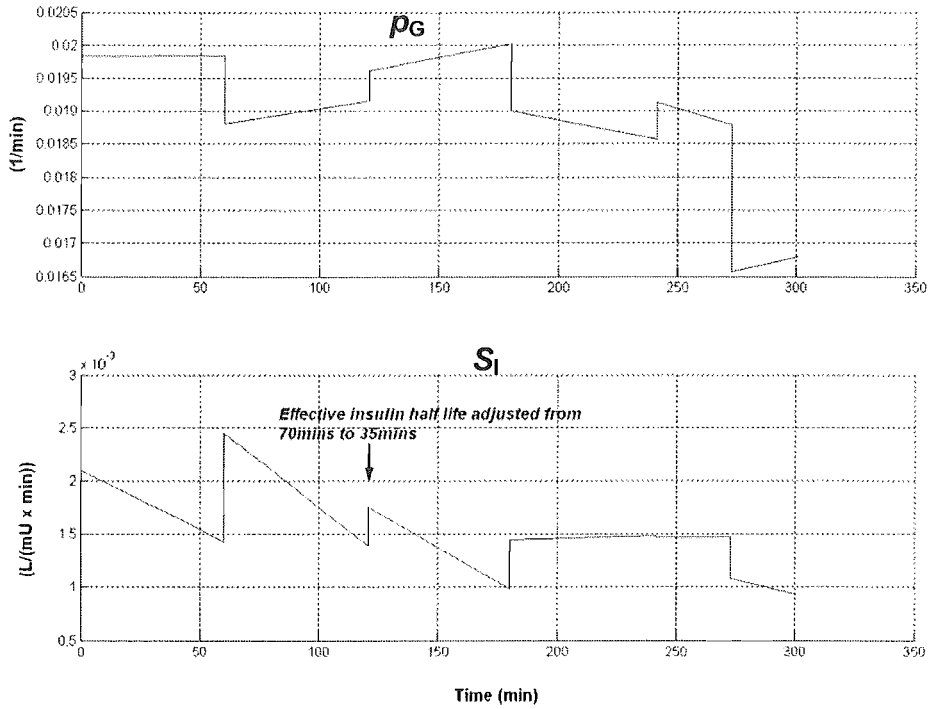


FIGURE 6.18: VARIATIONS IN PATIENT SPECIFIC PARAMETERS FOR TRIAL 6

This trial showed the impact of changing the insulin effective half-life, $k$, during a trial. The data collected from the first two hours resulted in a saw-tooth shape for insulin sensitivity, as shown in Figure 6.18, similar to that in trial 5. Due to modifications before the trial began, the effective insulin half-life was manually updated to 35 minutes, half of the original value, at 120 minutes into the trial. The effect of this change is seen in Figure 6.18 where $S_I$ loses its variability after 180 minutes and becomes more physiologically realistic.

The 'scalloped' shape of the glucose profile following an insulin bolus seen in Figure 6.17, resulted in the time between boluses being reduced to 30 minutes at 240 minutes into the trial, and hence 2 targets for that hour are shown instead of one. Table 6.7 shows the error between the targets and the achieved glucose values. Although the controller was effective

at reaching this half-hourly subtarget, the targets on either side were poor fits in comparison.

TABLE 6.7: COMPARISON BETWEEN TARGET AND ACHIEVED GLUCOSE LEVELS FOR TRIAL 6

| Time (min) | Target Glucose (mmol/L) | Achieved Glucose (mmol/L) | Error %(abs) |
|---|---|---|---|
| 120 | 9.82 | 9.10 | 7 % (-0.62) |
| 180 | 8.34 | 8.75 | 5 % (0.41) |
| 240 | 7.09 | 6.00 | 15 % (-1.09) |
| 270 | 6.52 | 6.85 | 5 % (0.33) |
| 300 | 6.00 | 7.20 | 20 % (1.20) |

## 6.4 CLINICAL TRIAL CONCLUSIONS

The clinical trials presented show the efficacy of the control algorithm and system models in achieving targeted glucose control across a wide range of critically ill patients. The progression of the model throughout the trials has shown merit in each change made to the model and control method. Ideally, a larger patient cohort will be tested using the current model to further analyse its effectiveness and find areas in which additional improvements could be made. Overall, the system model presented was able to accurately capture the essential dynamics exhibited.

The first two trials demonstrated the use of the system model and enhancements proposed by Doran et al (2004a; 2004b) and Chase et al (2003). The next two trials showed improved results and were able to achieve glucose targets more effectively, with target errors of 1 – 17 % (0.10 – 1.31 mmol/L). The robustness of the model and its ability to deal with unknown external perturbations was shown in the fourth patient. Finally, both trials showed the model's adaptive learning as the trial progressed, with errors between actual and predicted glucose levels reducing over time.

The fifth trial showed the largest improvement in model and control performance, with the addition of insulin appearance and glucose clearance saturation. The results showed almost perfect fits for the first four hours of the trial. The difference between targets and actual glucose values achieved ranged from 2 – 6 % or 0.10 – 0.43 mmol/L, which shows very tight targeted control with errors within the measurement error of 7 % (Arkray Inc. 2001). From this trial, the validity of the insulin appearance saturation was justified, however

glucose clearance saturation seemed to inhibit the model's ability to achieve a good fit to measured data, and so additional trials are required to better estimate this model parameter value.

The sixth trial showed good accuracy, but was unable to successfully achieve two of its targets, missing by 15 and 20 %. The addition of a manual adjustment to the effective half-life, suggested by the outcome of trial 5, was shown to be effective and removed the non-physiological saw- tooth shape from the fitted insulin sensitivity profile. Future work should consider the optimisation of the effective half-life, $k$, as well as the glucose clearance, $p_G$, and insulin sensitivity, $S_I$.

## 6.5 REFERENCES

Arkray Inc. 2001. "Glucocard™ Test Strip 2 Data Sheet. Japan: Arkray Inc.

Bergman, R. N., Finegood, D. T. and Ader, M. 1985. Assessment of Insulin Sensitivity in Vivo. *Endocr Rev.* 6(1): 45-86

Chase, J. G., Lam, Z. H., Lee, J. Y. and Hwang, K. S. (2002). Active Insulin Infusion Control of the Blood Glucose Derivative. Proc *Proc. of the 7th International Conf on Control, Automation, Robotics and Vision (ICARCV 2002)* in Singapore.

Chase, J. G., Shaw, G. M., Doran, C. V., Hudson, N. H. and Moorhead, K. T. (2003). Derivative Weighted Active Insulin Control Algorithms and Trials. Proc *IFAC Symposium* in Melbourne, Australia.

Derouich, M. and Boutayeb, A. 2002. The Effect of Physical Exercise on the Dynamics of Glucose and Insulin. *J Biomech.* 35(7): 911-917

Doran, C. V., Chase, J. G., Shaw, G. M., Moorhead, K. T. and Hudson, N. H. 2004a. Automated Insulin Infusion Trials in the ICU. *Diabetes Technology and Therapeutics.* 6(2)

Doran, C. V., Moorhead, K. T., Hudson, N. H., Chase, J. G. and Shaw, G. M. 2004b. Derivative Weighted Active Insulin Control Modelling and Clinical Trials for ICU Patients. *Med Eng Phys.* -to appear

Duncan, G. E., Perri, M. G., Theriaque, D. W., Hutson, A. D., Eckel, R. H. and Stacpoole, P. W. 2003. Exercise Training, without Weight Loss, Increases Insulin Sensitivity and Postheparin Plasma Lipase Activity in Previously Sedentary Adults. *Diabetes Care.* 26(3): 557-562

Furler, S. M., Kraegen, E. W., Smallwood, R. H. and Chisholm, D. J. 1985. Blood Glucose Control by Intermittent Loop Closure in the Basal Mode: Computer Simulation Studies with a Diabetic Model. *Diabetes Care.* 8(6): 553-561

Hovorka, R., Shojaee-Moradie, F., Carroll, P. V., Chassin, L. J., Gowrie, I. J., Jackson, N. C., Tudor, R. S., Umpleby, A. M. and Jones, R. H. 2002. Partitioning Glucose Distribution/Transport, Disposal, and Endogenous Production During IVGTT. *Am J Physiol Endocrinol Metab.* 282(5): E992-1007

Kraegen, E. W. and Chisholm, D. J. 1984. Insulin Responses to Varying Profiles of Subcutaneous Insulin Infusion: Kinetic Modelling Studies. *Diabetologia.* 26(3): 208-213

Natali, A., Gastaldelli, A., Camastra, S., Sironi, A. M., Toschi, E., Masoni, A., Ferrannini, E. and Mari, A. 2000. Dose-Response Characteristics of Insulin Action on Glucose

Metabolism: A Non-Steady-State Approach. *Am J Physiol Endocrinol Metab.* 278(5): E794-801

Rizza, R. A., Mandarino, L. J. and Gerich, J. E. 1981. Dose-Response Characteristics for Effects of Insulin on Production and Utilization of Glucose in Man. *Am J Physiol.* 240(6): E630-639

Turnheim, K. and Waldhausl, W. K. 1988. Essentials of Insulin Pharmacokinetics. *Wien Klin Wochenschr.* 100(3): 65-72

Wilinska, M. E., Chassin, L. J., Schaller, H. C., Pieber, T. R. and Hovorka, R. (2003). Modelling Insulin Lispro Kinetics During Physiological Conditions in Subjects with Type 1 Diabetes Treated by CSII. Proc *World Congress on Biomedical Engineering and Medical Physics* in Sydney, Australia. 24-29 August 2003.

# 7

# LONG-TERM MODEL VERIFICATION

## 7.1 MOTIVATION

Using data gathered in the retrospective audit of blood glucose levels in the Christchurch Hospital ICU gave the opportunity to verify the model, fitting procedure and patient parameters across a wide range of patients and over a longer time period than that used in the targeted control trials in Chapter 6. It also allowed closer observation of the variation of the patient specific parameters, $p_G$ and $S_I$, over time.

If the model dynamics can match the data with physiologically realistic parameter values over longer time periods, its use for control will be further validated. Any critically ill patient that requires glycemic control will likely need it for at least a couple of days. Hence, the controller and the model must be capable of realistically capturing a wide variety of patient dynamics over long time periods during which patient condition and parameters may vary significantly.

## 7.2 SYSTEM MODEL

Long term data fitting is performed using the model defined in Equations (3.19) – (3.21). This model includes the effect of endogenous insulin when the exogenous insulin infusion is low. The patient specific parameters, $p_G$ and $S_I$, are found using the identification routine described in Chapter 5. The bounds on the patient specific parameters, $p_G$ and $S_I$, are $0.01 \leq p_G \leq 0.02$ and $0.00001 \leq S_I \leq 0.0025$, respectively based on data in Chapter 4. The generic parameters are outlined in Table 7.1.

TABLE 7.1: GENERIC PARAMETERS FOR LONG-TERM DATA FITTING

| Parameter | Value |
|---|---|
| $V_I$ | 12 L |
| $n$ | 0.16 $min^{-1}$ |
| $k$ | 0.0099 $min^{-1}$ |
| $\alpha_G$ | 0.04 |
| $\alpha_I$ | $1.7 \times 10^{-3}$ |

The exogenous glucose input, $P(t)$, in Equation 3.21 changes with time, and is calculated from the feed details recorded on the patient's bedside chart. The exogenous insulin infusion, $u(t)$, in Equation 3.23, is also obtained from the patient's bedside chart.

## 7.3 PATIENT SELECTION

A random selection of patients from the 201 patient data audit with a period greater than one day with intervals between measured data points of three hours or less were used for the long-term data fitting. The data density of three hours was selected to ensure enough measurements to enable a good model evaluation. The entire length of stay was not always considered, as many patients only had a shorter period of data that fitted the criteria.

TABLE 7.2: PATIENTS SELECTED FOR LONG-TERM DATA FITTING

| Patient Number | Medical Subgroup | APACHE II Score | Age | Sex | Mortality | Diabetes |
|---|---|---|---|---|---|---|
| 24 | Other Medical | 25 | 47 | M | Y | Type 1 |
| 87 | Other Medical | 26 | 62 | F | | |
| 130 | Trauma | 11 | 21 | M | | Type 1 |
| 229 | Cardiac | 15 | 73 | F | | |
| 289 | Cardiac | 18 | 70 | M | | |
| 468 | General Surgical | 32 | 76 | M | | |
| 484 | Other Medical | 34 | 30 | F | | |
| 486 | General Surgical | 22 | 76 | F | | Type 2 |
| 519 | General Surgical | 29 | 69 | M | | Type 2 |
| 554 | Other Medical | 26 | 20 | F | | Type 1 |
| 666 | Cardiac | 8 | 44 | F | | Type 2 |
| 847 | Other Medical | 17 | 67 | F | | |
| 1016 | General Surgical | 20 | 37 | F | | Type 2 |
| 1025 | Pulmonary | 36 | 48 | M | | Type 2 |
| 1090 | General Surgical | Unknown | 37 | F | | |
| 1099 | Pulmonary | Unknown | 24 | M | Y | |
| 1125 | Other Medical | Unknown | 72 | F | Y | |

The medical subgroup, APACHE II score, age, sex, mortality and diabetic classification are shown in Table 7.2. Due to the density of data required, eight of the seventeen patients selected turned out to be diabetic individuals. Patients with a pre-described condition of diabetes are likely to have their blood glucose levels monitored more closely. Most of the patients are from the 'General Surgical' or 'Other Medical' subgroups, and there is a wide range of APACHE II scores and ages (8 - 36 and 20 – 76, respectively). Overall, this subset broadly represents the cross section seen in the ICU.

## 7.4 ERROR METRIC

The percentage error between the fit and the data was calculated for each data point.

$$e_i = \left| \frac{G_{fit}(t_i) - G_{data}(t_i)}{G_{data}(t_i)} \right| \times 100 \qquad 7.1$$

Table 7.3 shows the mean and standard deviation of the percentage error calculated using Equation 7.1 for each patient. It also shows the time interval used for modelling and the number of measurements in this interval. The average percentage error was 4.39 % and the average standard deviation was 4.45 %. Patient 1090 had the smallest percentage error and standard deviation, while patient 289 had the largest standard deviation and the second largest percentage error. Even the highest percentage fitting error of 7.6 % is still relatively low compared to the 7 % measurement error of the GlucoCard™ (Arkray Inc. 2001). There was no correlation between there is no correlation between mean fit error and frequency of measurement for this regularly sampled cohort.

TABLE 7.3: ERROR IN DATA FITTING

| Patient Number | Mean Percentage Error (%) | Percentage Error Standard Deviation (%) | Time Interval (days) | Number of Measurements | |
|---|---|---|---|---|---|
| | | | | Total | Per Day |
| 24 | 4.78 | 6.90 | 2.0 | 32 | 1.6 |
| 87 | 2.38 | 2.70 | 6.4 | 48 | 7.5 |
| 130 | 7.62 | 6.07 | 1.4 | 31 | 22 |
| 229 | 5.83 | 9.75 | 10.0 | 78 | 7.8 |
| 289 | 7.11 | 7.75 | 1.7 | 13 | 7.7 |
| 468 | 3.17 | 3.03 | 1.7 | 17 | 10.0 |
| 484 | 2.53 | 2.00 | 1.7 | 18 | 10.6 |
| 486 | 3.17 | 3.03 | 1.6 | 16 | 10.0 |
| 519 | 3.08 | 2.52 | 12.3 | 82 | 6.7 |
| 554 | 5.24 | 4.56 | 2.3 | 40 | 17.4 |
| 666 | 3.68 | 2.28 | 1.6 | 15 | 9.4 |
| 847 | 4.68 | 4.32 | 1.5 | 12 | 8 |
| 1016 | 4.11 | 5.17 | 1.6 | 13 | 8.1 |
| 1025 | 4.26 | 4.05 | 1.7 | 15 | 8.8 |
| 1090 | 1.03 | 0.93 | 1.6 | 10 | 6.3 |
| 1099 | 4.70 | 3.82 | 1.6 | 14 | 8.3 |
| 1125 | 3.61 | 2.89 | 1.7 | 11 | 6.5 |
| **Average** | **4.39** | **4.45** | **3.1** | **27.4** | **12.6** |

## 7.5 PATIENT FITTING EXAMPLES

### *7.5.1 Low Fitting Error Cases*

Patient 1090 had the lowest fitting error and standard deviation of those patients considered, representing the best overall fit. Over the 1.6 days considered of the patients 7-day stay, the insulin infused was constant at 1 U/hr, and the feed was constant at 0.0247 mol/(L· min). Figure 7.1 shows a relatively constant normoglycemic profile over this time with low variations in insulin sensitivity, $S_I$, showing that the patient was very stable and hence, not overly difficult to fit.

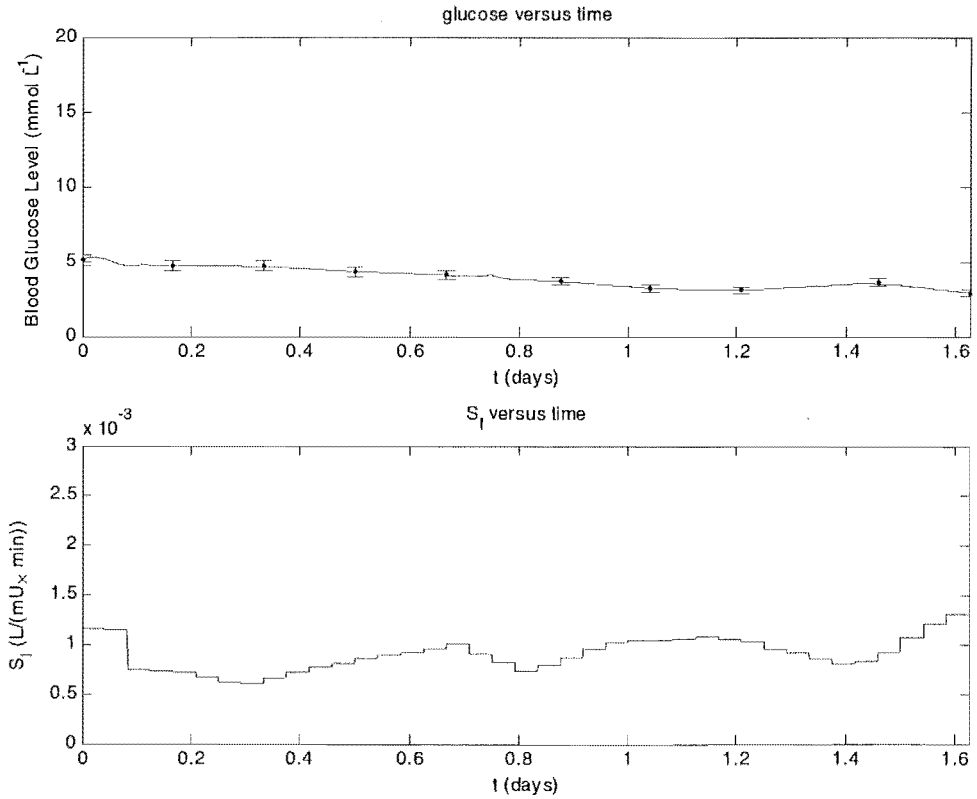


FIGURE 7.1: PATIENT 1090 DATA FIT

Patient 87 had a length of stay of 35 days, and over six consecutive days had sufficient data measurements the model fitting. Unlike the patient 1090, the glucose level is much more variable, leading to a higher variability and range in the insulin sensitivity, $S_I$. The glucose clearance, $p_G$, is stable over most of the time considered at 0.01 $min^{-1}$, but does reach values of up to 0.015 $min^{-1}$. These values are well within the physiological range expressed in the literature, and show a change in the metabolic responses at these time periods. Over the six days shown in Figure 7.2, the insulin infusion is shown in Figure 7.2 and the feed varied between a very low rate and the standard feed of 0.0918 mmol/(L· min) as shown in Figure 7.3. Figure 7.2 shows some form of cyclical response, with a cycle occurring with a period of just over two days, overlaid with a smaller cycle period of approximately six hours. There does not appear to be any consistent correlation between $S_I$ and the feed or insulin profiles.

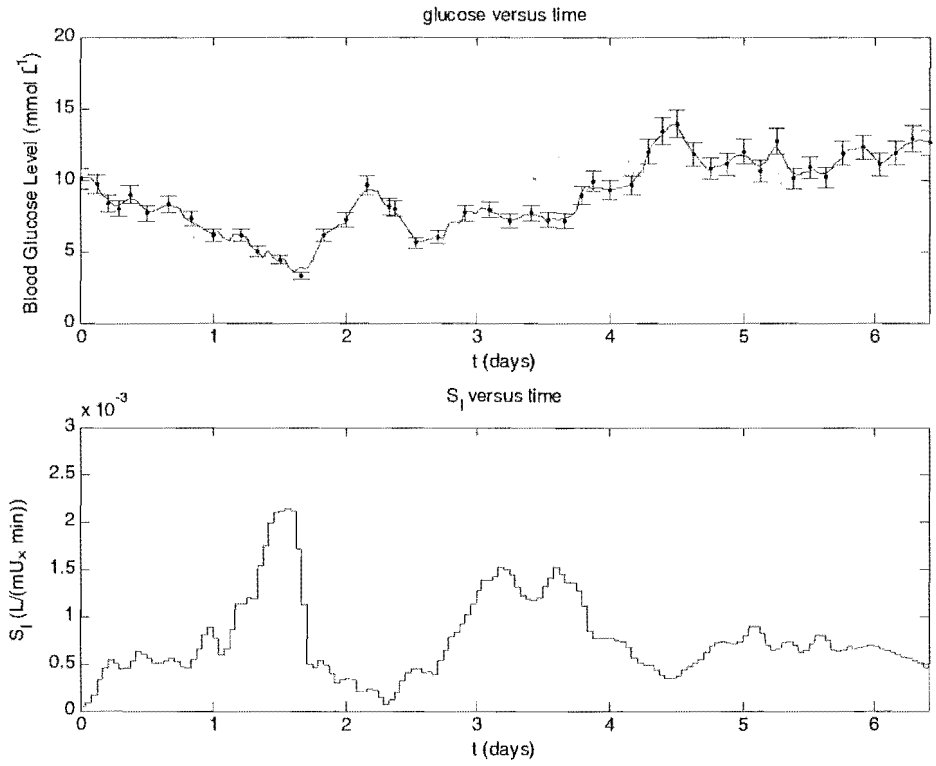


FIGURE 7.2: PATIENT 87 DATA FITTING

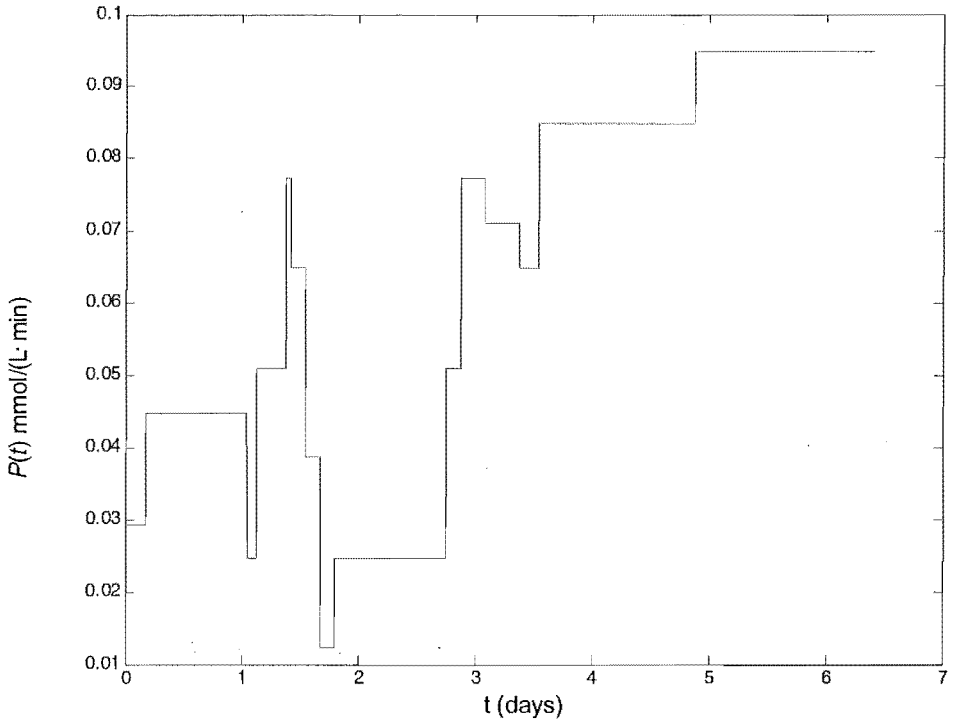


FIGURE 7.3: PATIENT 87 FEED DETAILS

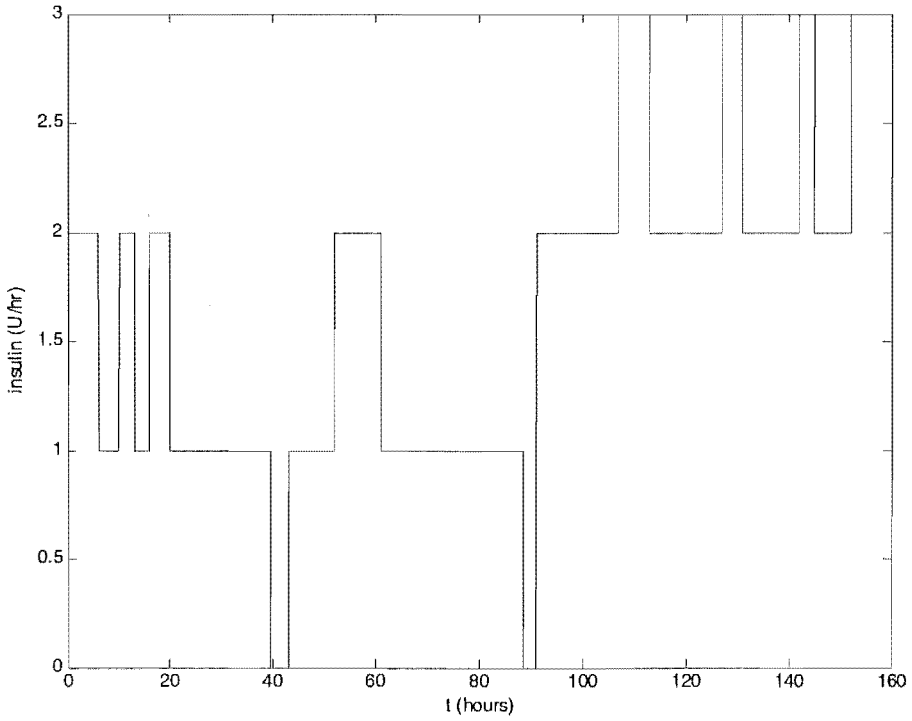


FIGURE 7.4: PATIENT 87 INSULIN DETAILS

The ability of the model to have very low errors on these two very different patients is promising. The 1.6 and 6.2 day periods also represent very long stretches for model fitting compared to the few other published results (Hovorka, et al., 2002). Finally, the average error of 1.7 % represents a very good fit given the measurement error.

### *7.5.2 High Fitting Error Cases*

The worst fits have an average error of 7.6 %. While this number is still acceptable for use in clinical situations, the reasons for poorer fit should be examined. Patient 130 is a Type 1 diabetic individual, and hence had glucose measurements taken almost every hour as shown in Figure 7.5. This patient had relatively low insulin sensitivity and large and continuous insulin infusions were required to achieve normoglycemic over one day, as shown in Figure 7.6.

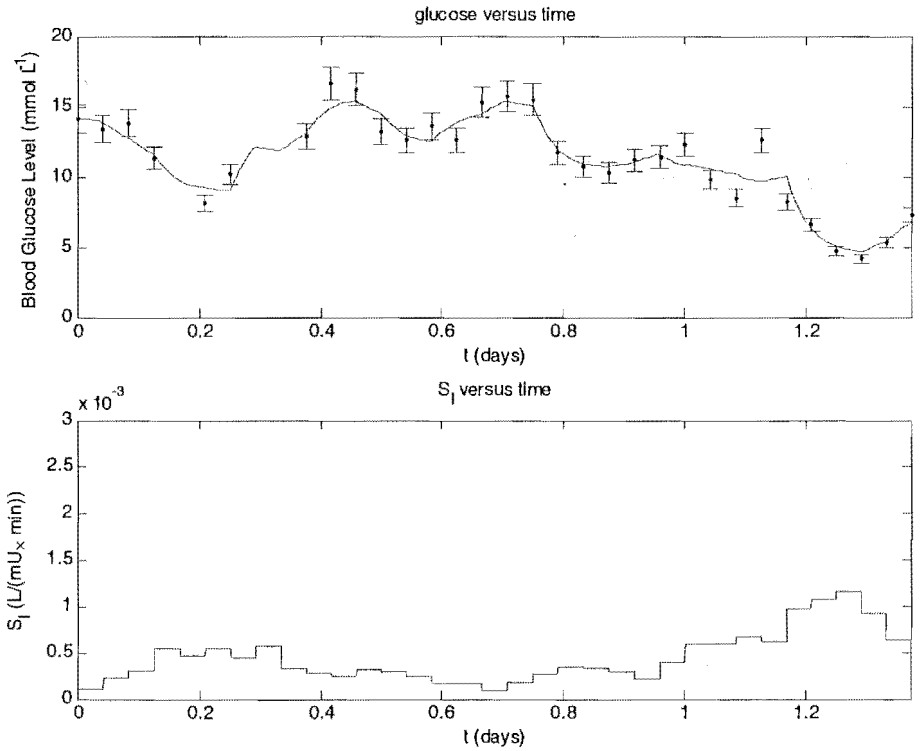


FIGURE 7.5: PATIENT 130 DATA FITTING

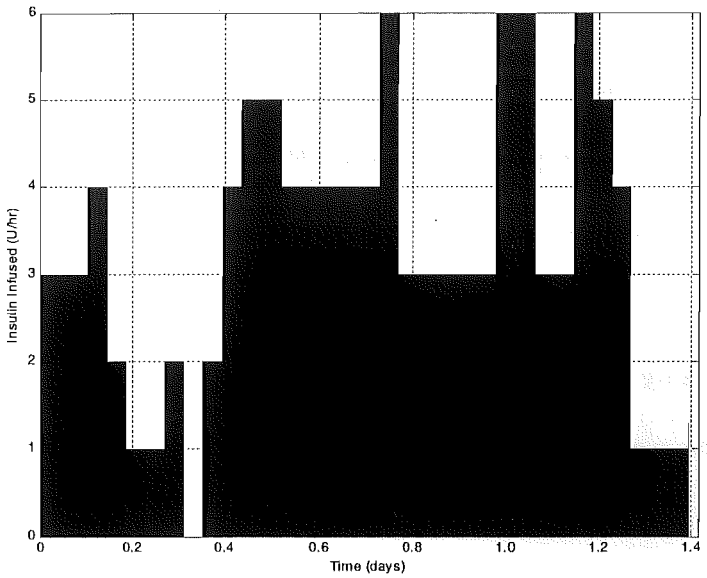


FIGURE 7.6: INSULIN INFUSION PROFILE OVER DATA FITTING PERIOD FOR PATIENT 130

Although the model captures the large majority of blood glucose measurements throughout, it does miss a few data points at the peaks and troughs of the blood glucose profile. The blood glucose measurement of 12.3 mmol/L at 1.04 days was at first thought to be an error, but is probably the result of the insulin infused changing from 6 U/hr to 3 U/hr and back again during this time. Another problem in the data gathered is that the hourly blood glucose readings and insulin infusions, may not actually have occurred on the hour as is assumed in the model fits. The bedside charts give the nurses one space for each half an hour to record the blood glucose measurement and insulin infusion, and in the recording for the retrospective data audit, blood glucose and insulin infused were recorded hourly. Thus the values assumed to occur on the hour, might actually have occurred at any time during that hour, leading to discrepancies between modelling and actual data. Despite these problems, it can be seen that the larger error for patient 130 is largely due to 2-4 measurements with large errors over the 1.3 days fitted.

Patient 289 showed a less volatile glucose response curve, but still had a reasonably high percentage error. The main area of error occurred at the sudden blood glucose drop at 0.88 days. The model was unable to capture the drop from 8.8 mmol/L to 3.4 mmol/L in four hours then back to 6.6 mmol/L two hours later. This 5.4 mmol/L drop was the result of increased insulin infusion from 1 to 2 U/hr immediately following the 8.8 mmol/L measurement. The infusion was then turned off following the possible hypoglycemic episode, resulting in glucose cycling and poor management. The feed stayed relatively constant during this time. However, the model still captured the basic trend in this area, and the large percentage error is a result of the smoothing of patient specific parameter fits to avoid sudden non-physiological changes.

Overall, the fits at both ends of the scale are very good. Where larger errors are seen, so too are larger standard deviations, indicating the presence of a few measurements with larger errors, as seen in Figure 7.7. Finally, there is always the possibility that some measurements are contaminated or otherwise in error where some of the larger errors occur, particularly if the measurement is a relatively high or low value for the patient. However, it bears repeating that tall fits over this diverse group were at or within measurement error, indicating that the very simple model defined is capable of capturing the dynamics observed.

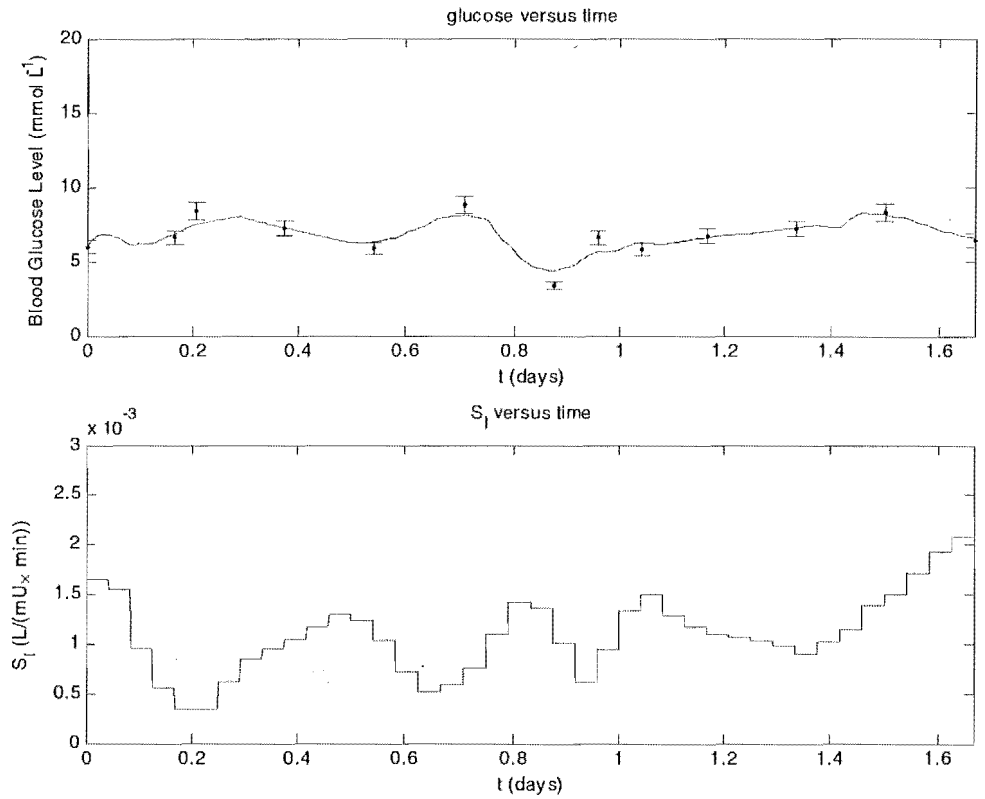


FIGURE 7.7: PATIENT 289 DATA FITTING

## 7.6 MODEL PREDICTION

It is not enough to capture dynamics by fitting, the model must also be able to predict upcoming behaviour and trends at least 1 – 2 hours ahead for use in central. A model that fits observed dynamics well and provides good predictions is well verified for clinical control applications presented.

Patients 24, 130 and 554 were used to test prediction capabilities of the model. These patients were chosen because they had a number of measurements one hour apart to measure predictive quality at any point. To make a forward prediction from a given point, the model fit from the data of the previous eight hours was used. Note that predictions are insensitive to the length of time fitted prior to prediction as long as it is greater than two hours or 3 – 4 measurements. The prediction is made by holding the current patient specific parameters, $p_G$ and $S_I$, and the equilibrium glucose level, $G_E$, constant over the next four hours. The model value is then compared to the actual data for these four hours and the percentage error, $e_i$, is calculated at one, two, three and four hours

$$e_i = \left| \frac{G_{fit\_prediction}(t_i) - G_{data}(t_i)}{G_{data}(t_i)} \right| \times 100 \tag{7.2}$$

These time periods are chosen to represent the range of time over which control might be exerted without measurement.

### *7.6.1 Patient 24 Prediction Results*

Figure 7.8 shows an example of one of the predictions made from an eight hour window. As this patient's blood glucose was decreasing and the patient specific parameters, pG and SI, were held constant as shown in Figure 7.9, the general trend has been missed by the model in this prediction. The data between 1500 and 2700 minutes was used for making predictions, and the prediction errors calculated using Equation (7.2) were dependent on the variability of the glucose data.

Table 7.4 shows the average prediction errors one, two, three and four hours ahead, and their standard deviations, for 16 sets of predictions obtained from each hour between 1500 and 2460 minutes. The prediction error increased with increasing prediction time interval as expected, and shown in Table 7.4. The errors range from 6.77 % to 14.56 %.

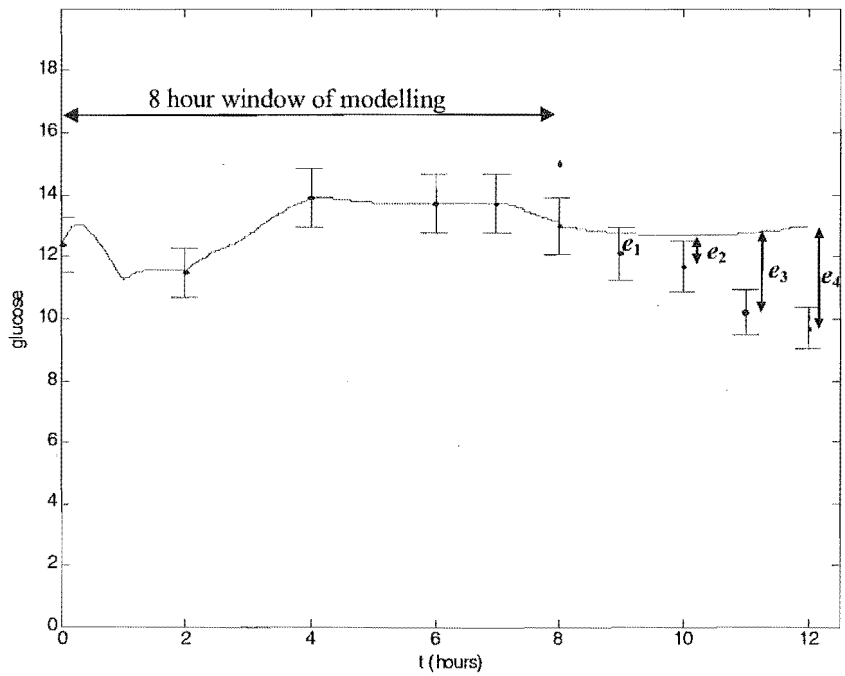


FIGURE 7.8: PATIENT 24 PREDICTION EXAMPLE

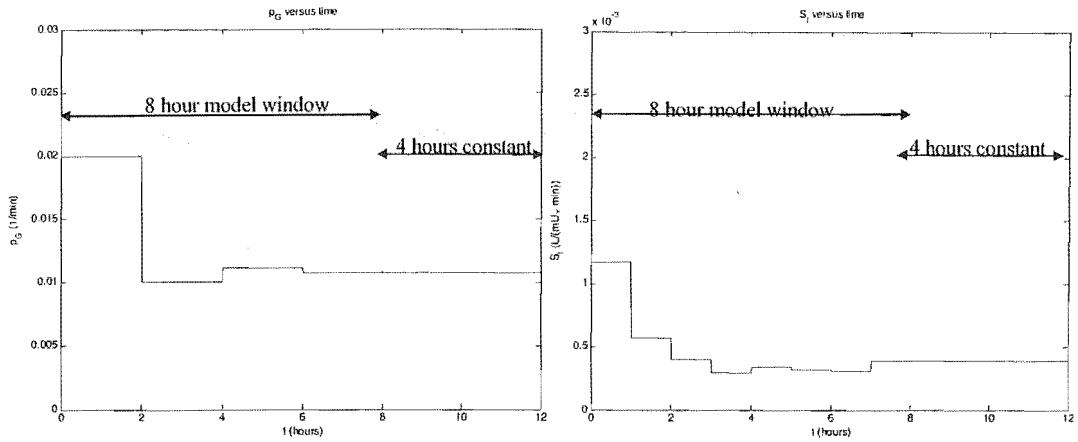


FIGURE 7.9: PATIENT 24 SPECIFIC PARAMETERS FOR PREDICTION, GLUCOSE CLEARANCE (LEFT) AND INSULIN SENSITIVITY (RIGHT)

TABLE 7.4: PATIENT 24 PREDICTION ERRORS

| Prediction Error | Prediction Time (hours) | Average Prediction Error (%) | Error Standard Deviation (%) |
|---|---|---|---|
| $e_1$ | 1 | 6.77 | 4.68 |
| $e_2$ | 2 | 7.34 | 6.67 |
| $e_3$ | 3 | 14.15 | 7.77 |
| $e_4$ | 4 | 14.56 | 11.71 |

### *7.6.2 Patient 130 Prediction*

Patient 130 had a more variable glucose profile than patient 24 during the eight hour window leading up to the prediction period shown as an example in Figure 7.10. The variability was high throughout the 720 to 1740 minutes used for prediction testing, and this variability is reflected by higher error values and standard deviations in Table 7.5.

TABLE 7.5: PATIENT 130 PREDICTION ERRORS

| Prediction Error | Prediction Time (hours) | Average Prediction Error (%) | Error Standard Deviation (%) |
|---|---|---|---|
| $e_1$ | 1 | 10.92 | 10.02 |
| $e_2$ | 2 | 15.87 | 15.46 |
| $e_3$ | 3 | 19.55 | 15.34 |
| $e_4$ | 4 | 22.97 | 19.33 |

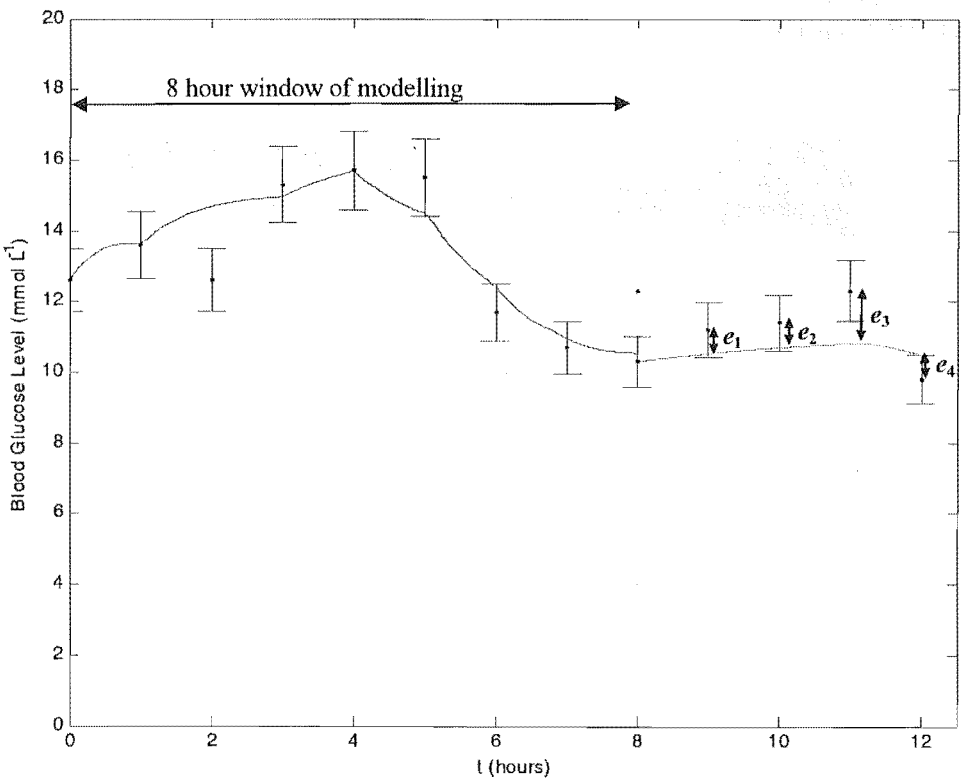


FIGURE 7.10: PATIENT 130 PREDICTION EXAMPLE

### *7.6.3 Patient 554 Prediction*

Patient 554 also had a reasonably variable glucose profile throughout the 2.3 days fitted, as shown by the relatively high errors and standard deviations in Table 7.6. Figure 7.11 shows a period of the 1200 minutes used for prediction that has relatively small errors due to the stability in the glucose profile at that time.

TABLE 7.6: PATIENT 554 PREDICTION ERRORS

| Prediction Error | Prediction Time (hours) | Prediction Error (%) | Error Standard Deviation (%) |
|---|---|---|---|
| $e_1$ | 1 | 10.73 | 9.79 |
| $e_2$ | 2 | 16.90 | 12.69 |
| $e_3$ | 3 | 18.88 | 15.45 |
| $e_4$ | 4 | 22.13 | 18.21 |

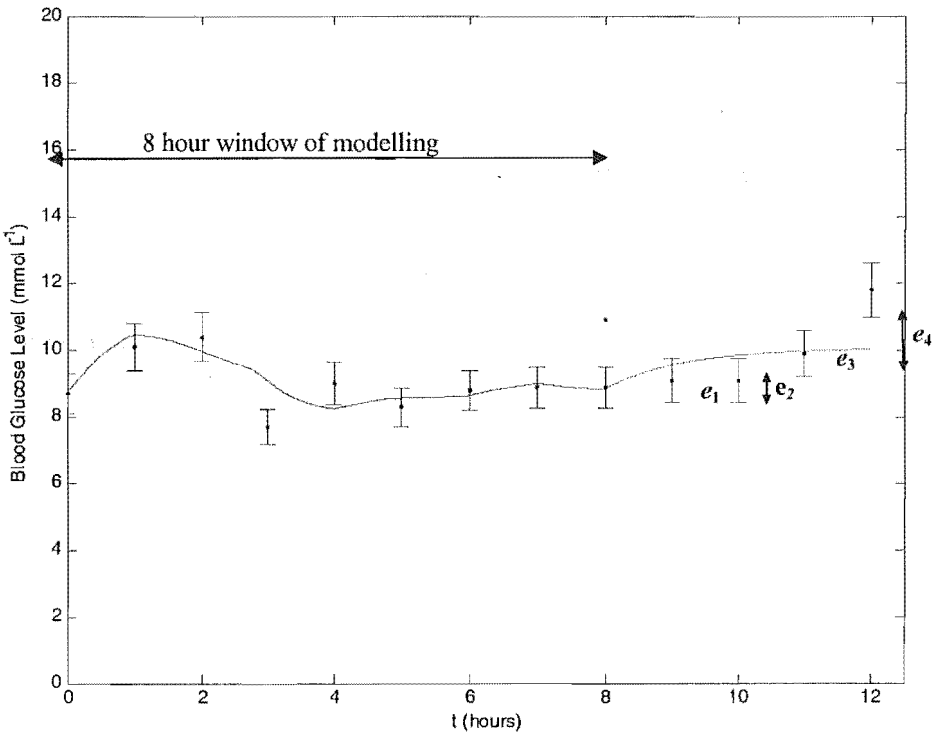


FIGURE 7.11: PATIENT 554 PREDICTION EXAMPLE

The average prediction errors shown in Table 7.4, Table 7.5 and Table 7.6 are close to the measurement error for the first hour. By holding the patient specific parameters, $p_G$ and $S_I$, constant when there is a known variation in insulin sensitivity, a compromise between insulin sensitivity rising and falling is made, reducing the worst case error of prediction from a trend. Overall, the predictive ability demonstrated is acceptable for tight control only over the first hour.

## 7.7 CYCLICAL VARIATION IN INSULIN SENSITIVITY

A number of researchers have explored the idea of variation in insulin sensitivity in ambulatory diabetic and normal individuals (e.g. Arasaradnam, et al., 2002; Radziuk, 2000; Wilinska, et al., 2003). To the author's knowledge, little is known about variations of insulin sensitivity in critically ill patients. By using the insulin sensitivity profiles from long-term data fitting of the 17 patients considered, any cyclical variations may be observed.

To find the period of a cycle in these patients, the average oscillation period of insulin sensitivity, $S_I$, must be determined. This value is obtained by finding the inflection points in the insulin sensitivity curve, $S_I(t)$, and averaging the distance between every second inflection point. An inflection point is where the second derivative is zero. To find inflection points in this noisy data, the insulin sensitivity curve, $S_I(t)$, is low pass filtered, as shown in Figure 7.12, where every second inflection point is shown by a 'o'. Patient 519 in

Figure 7.12 has a mean cycle length of 0.49 days (approximately 12 hours), and a standard variation of 0.10 days (approximately 2 – 3 hours).

The mean and standard deviations of the cycle lengths for each patient are found in Table 7.7, along with the number of cycles found in their data. The range in cycle length is 0.23 – 0.54 days (5.5 – 13.0 hours). Taking into account the number of cycles for each patient, the average period over all the patients is 0.45 days (10.8 hours) which is very close to half a day, suggesting a half day cycle in critically ill patients.

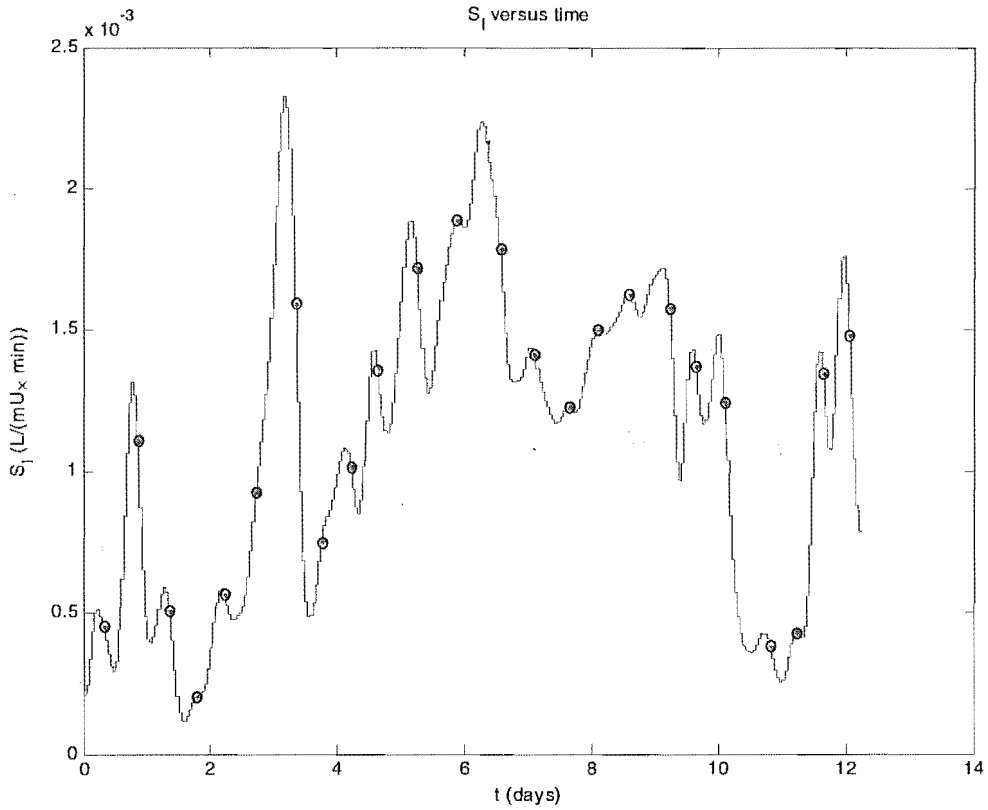


FIGURE 7.12: PATIENT 519 SMOOTHED INSULIN SENSITIVITY SHOWING EVERY SECOND INFLECTION POINT

TABLE 7.7: CYCLICAL VARIATIONS IN INSULIN SENSITIVITY

| ICU Patient Number | Mean Cycle Period (days) | Cycle Standard Deviation (days) | Number of Cycles |
|---|---|---|---|
| 24 | 0.54 | 0.17 | 3 |
| 87 | 0.50 | 0.12 | 12 |
| 130 | 0.23 | 0.03 | 2 |
| 229 | 0.42 | 0.16 | 23 |
| 289 | 0.40 | 0.10 | 3 |
| 468 | 0.43 | 0.17 | 3 |
| 484 | 0.40 | 0.10 | 3 |
| 486 | 0.52 | 0.03 | 2 |
| 519 | 0.49 | 0.10 | 24 |
| 554 | 0.46 | 0.11 | 4 |
| 666 | 0.46 | 0.11 | 3 |
| 847 | 0.35 | 0.15 | 2 |
| 1016 | 0.42 | 0.07 | 3 |
| 1025 | 0.29 | 0.06 | 2 |
| 1090 | 0.54 | 0.06 | 2 |
| 1099 | 0.46 | 0.06 | 2 |
| 1125 | 0.32 | 0.02 | 3 |

## 7.8 CONCLUSIONS

The long-term fitting results show great promise, as the model was accurately able to capture the measured data to within the measurement error of the sensor. The strength of this model is that it has been able to capture the observed dynamics to within a small error across a wide range of patients, including Type 1, Type 2 and non-diabetic individuals, as well a wide range of injuries and illnesses. Using mainly generic parameters and only two patient specific parameters the results show the power of this simple, non-linear model.

Predictions are to within 11 % in the first hour, and up to 23 % over four hours. This result is comparable to the ranges expected for 1 – 4 hour glucose variation obtained using the statistics presented in Chapter 2. Basically, if a measurement is to be accurate to within 10 %, it should be measured every hour. The prediction is more successful when the patient's glucose levels are in steady state, and hence the patient specific parameters, $p_G$ and $S_I$, are unlikely to change much. If the patient's glucose metabolism is changing as a result to an external perturbation to the system or their condition, then the predictions will not be as accurate, as expected

From this limited research, there appears to be a twice daily variation in insulin sensitivity in critically ill patients. An oscillatory period of between 0.42 and 0.54 days was observed over most of the 17 patients with an average of 0.45 days. Additional research is required to confirm this phenomenon and determine its cause.

## 7.9 REFERENCES

Arasaradnam, M. P., Morgan, L., Wright, J. and Gama, R. 2002. Diurnal Variation in Lipoprotein Lipase Activity. *Ann Clin Biochem.* 39(Pt 2): 136-139

Arkray Inc. 2001. "Glucocard™ Test Strip 2 Data Sheet. Japan: Arkray Inc.

Hovorka, R., Shojaee-Moradie, F., Carroll, P. V., Chassin, L. J., Gowrie, I. J., Jackson, N. C., Tudor, R. S., Umpleby, A. M. and Jones, R. H. 2002. Partitioning Glucose Distribution/Transport, Disposal, and Endogenous Production During IVGTT. *Am J Physiol Endocrinol Metab.* 282(5): E992-1007

Radziuk, J. 2000. Insulin Sensitivity and Its Measurement: Structural Commonalities among the Methods. *J Clin Endocrinol Metab.* 85(12): 4426-4433

Wilinska, M. E., Chassin, L. J., Schaller, H. C., Pieber, T. R. and Hovorka, R. (2003). Modelling Insulin Lispro Kinetics During Physiological Conditions in Subjects with Type 1 Diabetes Treated by CSII. Proc *World Congress on Biomedical Engineering and Medical Physics* in Sydney, Australia. 24-29 August 2003.

# 8

# CONCLUSIONS

## 8.1 THE NEED FOR CONTROL

The retrospective data audit of 201 patients that had a length of stay of greater than 72 hours in the Christchurch Hospital ICU over a 1 year period has shown the validity of developing a closed-loop control algorithm for clinical situations. The study showed that of the critically ill patients considered, 19 % had at least one glucose measurement above 15 mmol/L, which is potentially harmful. It was shown that a reduced mean, maximum and range of blood glucose levels were associated with reduced mortality so survivors were more likely to have lower values of these metrics than non-survivors ($P = 0.014$, $P = 0.001$ and $P = 0.003$, respectively).

The proportion of stay and average insulin infused both had a negative effect on mortality ($P = 0.02$ and $P = 0.01$, respectively). Hence, it is suggested that it is the reduction of glucose levels, not the insulin infusion that is beneficial to survival. As a result, future work will consider regulating hyperglycemia by controlling the dextrose input. Finally,

from retrospective observation of the glucose and insulin infusion data in these patients, the combination of intuitive control and the sliding scale protocol employed, leads to glucose cycling, which could be also eliminated by use of well-designed control.

The Christchurch Hospital protocol of measuring and recording blood glucose at least every four hours was often not followed. This result could occur because the clinical staff were too busy or did not see controlling blood glucose levels as a priority for the patient. The advance of blood glucose sensing devices will allow coupling glucose data with an insulin infusion system and control algorithm, freeing the clinical staff from some responsibility in this area to focus on other aspects of the patient's health. The fact that measurements were taken more frequently in non-survivors than survivors ($P = 0.03$) suggests that those patients in worse health were monitored more closely.

## 8.2 MODEL DEVELOPMENT

The model was developed from a simple two-compartment model to a more complex, yet more physiologically justified, non-linear model. This model accounts for non-linear saturation of exogenous insulin appearance rate and its saturable utilisation to reduce blood glucose levels. The addition of delayed insulin utilisation via a convolution integral has accounted for the accumulation dynamic seen in prior clinical trials, and better matches physiological knowledge.

Removing endogenous insulin production from the model reduced model complexity and improved model parameter fits in cases where exogenous insulin was infused. However, where there was no exogenous insulin the basal endogenous insulin term is still required. The addition of insulin appearance and glucose clearance saturation are physiologically justified, but require more clinical testing is required to determine whether the glucose clearance saturation is justified. The objective of keeping complexity to a minimum has been achieved, and the model has been shown to be proficient in both short-term and long-term fitting, as well as in clinical adaptive control applications.

## 8.3 PARAMETER VERIFICATION

An extensive literature review found a wide range of parameter values determined by many different methods. The challenge came in converting the values found in the literature into useful values or ranges for use in the system model. Patient specific parameters, $p_G$ and $S_I$, that are known to change over time, were assigned constraints in the fitting process of the system model to keep them within physiological ranges found in the literature, resulting in constraints of $0.01 \leq p_G \leq 0.02$ and $0.00001 \leq S_I \leq 0.0025$. Estimates for generic parameters, such as $\alpha_I$, $\alpha_G$, $k$ and $n$, were obtained, and later verified using both short-term and long-term retrospective data, as well as during clinical trials.

A novel method for identifying patient specific parameters is presented. This method utilises the integral of the glucose derivative equation to find the unknowns, $p_G$ and $S_I$. The result is a convex, computationally simple, linear, least squares solution.

## 8.4 TARGETED CONTROL

The clinical trials showed the efficacy of the adaptive control algorithm and system models in achieving targeted control across a range of critically ill patients. Targets were achieved in the final two trials with an average error of 4.25 %, which is well within the measurement error. Ideally, a larger patient cohort will be subjected to the current model in order to further analyse its effectiveness and find areas in which improvements could be made. The resulting model and controller must have high levels of robustness, and accurately capture the essential dynamics of the glucose-insulin metabolic system across a number of patients with various levels of insulin resistance and glucose intolerance.

## 8.5 LONG TERM DATA FITTING

The parameter identification method developed shows great promise for drug therapy control algorithms. The model was accurately able to capture the dynamics in the measured data to within the 7 % measurement error of the sensor. From this limited research, there also appears to be an oscillation in insulin sensitivity in critically ill patient with a period of approximately half a day. Additional research may be required to confirm this phenomenon.

Predictions are to within 11 % in the first hour, and up to 23 % over four hours. The prediction is more successful when the patient's glucose levels are in steady state, and hence the patient specific parameters, $p_G$ and $S_I$, are unlikely to change much. Overall, the

predictive ability demonstrated by the model and parameter fitting is acceptable for tight control only over the first hour.

## 8.6 SUMMARY

This research has successfully quantified hyperglycemia in critically ill patients showing the need for glucose control in critically ill patients. The relatively simple system model developed effectively captures the essential dynamics of the glucose-insulin metabolism, over short and long term periods, and provides a foundation for developing semi-automated control protocols. The level of existing and emerging technology allows a closed-loop automated system to be realised for tight glycemic control in closely monitored clinical situations. Overall, the research presented is a significant step towards fully automated adaptive control of hyperglycaemia in critically ill patients.

# 9

# FUTURE WORK

## 9.1 INTRODUCTION

Although the thesis presented has covered a wide range of modelling, literature reviews, data analysis and clinical trials, it has not been extensive enough to cover a number of the questions and objectives proposed. The ultimate objective of the research is to develop a medical control system that can be used to control glycemic levels in both clinical situations and ambulatory patients. To achieve this goal, extensive modelling and testing is required, justifying the models and control methods utilised.

## 9.2 MODEL DEVELOPMENT

Modelling of the glucose regulatory system should have a greater focus on patient variability and robustness, while maintaining the simplicity that ensures its use in clinical situations and that minimal computational power is required. A range of clinical and retrospective trials should be used to verify model improvements. It is also hoped that the

model can be extended to include other metabolic processes, both within and outside the glucose-insulin response system.

The existing intravenous two-compartment model could be used in conjunction with Markov simulations to determine the impact of the variability of patient specific parameters, $p_G$ and $S_I$. By using Markov simulations, the tendency of one event to be followed by another is analysed, and hence Markov simulations can be used to find the extent of the variation in patient specific parameters using retrospective data. The addition of a stochastic component to the glucose clearance and insulin sensitivity parameters, $p_G$ and $S_I$, will create models that more accurately capture these variations, resulting in an increased robustness in the controller that will increase it's accuracy across a wider population of patients. The overall goal of this effort would be to design models and controllers with broader applicability – a 'one size fits all' goal.

The same model could also be used as a basis for controlling glycemic levels by varying glucose, rather than insulin, infusions. Although the system model already accounts for an external glucose input, $P(t)$, the accuracy of the dynamics involved in transportation and loss of glucose have not been closely examined using this model. Parameters such as external glucose input, $P(t)$, glucose clearance, $p_G$, and glucose clearance saturation, $\alpha_G$, will have to be scrutinised, and the trade-offs between glucose clearance, $p_G$, and insulin saturation, $S_I$, will probably become more apparent.

The model will need to be extended for use in both ambulatory patients and clinical patients without arterial lines. It will therefore need to consider transportation delays and losses of insulin through the sub-cutaneous layer. As a result, the two-compartment model used for intravenous insulin infusions may be converted back to a three-compartment model similar, but with increased complexity, to that of Bergman et al (1985). Both ambulatory patients and clinical patients are likely to be receiving glucose as a meal input with a variety of food that break down into glucose in different ways, unlike the majority of critically ill patients that receive an almost constant feed infusion, and so the log-normal glucose input, *P(t)*, proposed by Lam et al (2002) and used by Doran et al (2004a; 2004b) and Chase et al (2003) in clinical trials will have to be re-evaluated.

Finally, as the glucose-insulin system model is very similar to those in a variety of pharmacodynamic systems, the general modelling and control methods developed in the proposed research may be extended to these similar systems. Such systems may include the agitation-sedation cycle in sedated ICU patients and the administration of certain antiviral drugs.

## 9.3 CONTROLLER DEVELOPMENT

Controllers employed to date in conjunction with this model have included heavy derivative control (Chase, et al., 2002; 2003; Doran, et al., 2004a; 2004b; Lam, et al., 2002) and sub-target control (work unpublished) using intravenous insulin infusions. It is envisioned that future work may employ both these control regimes and involve the

development of others. The main aim of control development is to produce an efficient controller that is highly robust to variations between patients. The adaptive controller, as used in this thesis to achieve sub-targets, is likely the method that will be used for control in the near future. This method will be tested with both retrospective data and in a clinical environment, probably in the ICU.

This year will also see the introduction of varying glucose infusions as a method to achieve set sub-targets. Research has shown that enteral feeding in critically ill patients often gives excess to requirements (Patino, et al., 1999; Weissman, 1999; Woolfson, 1980), and by using a constant insulin infusion and changing the input of dextrose into the human glucose-insulin system, the method of control has been reversed. The results of both insulin and glucose controlled glycemic levels may well be used in conjunction in the future to achieve optimal control of blood glucose levels in critically ill patients.

## 9.4 CLINICAL TRIALS

It is expected that the research focus in the future will remain on critically ill patients, as due to the technology development and legal issues, it is likely that a clinical environment is the first place an automated glucose control unit will be implemented. The results obtained from both clinical trials and retrospective data on ICU patients can easily be extended to other hospital situations, such as cardiac, paediatric and post-operative critical care, as well as for diabetic patients in the wards.

The data gathered from the retrospective audit of the Christchurch Hospital ICU over one year, gives a wealth of patient data for use in model and parameter verification. Future work may include the addition of more retrospective data to this subset, from both the Christchurch Hospital ICU and other hospitals, as a number of other researchers are considering similar retrospective trials.

As well as hyperglycemic critically ill patients, future work should also consider supra-glycemic diabetic keto-acidosis patients (DKA's). These patients are admitted to hospital in a coma-like state as a result of extremely high glucose levels, and due to their sensitive nature, the glucose control is best done in steps over a period of time. This situation is ideally suited to the sub-target adaptive controller already in use in clinical trials, and is a potential future application for the work developed here.

To test the addition of the effects of subcutaneous insulin infusion, retrospective data is also available from the Christchurch Hospital Lipids and Diabetes Research Group. This data is from OGTT's on Type 1 and Type 2 diabetic individuals. There may also be scope to test the subcutaneous model and parameters developed on ambulatory patients.

## 9.5 COMMERCIAL VIABILITY

The future of this research all ends in a final commercial product. As well as the research to be undertaken, there are a number of other factors involved in getting a product to market. The glucose controller mechanism will have to go through stages such as design

prototyping, reliability testing and market research. The commercial viability in both clinical and ambulatory situation will obviously need to be considered in research development models in future.

## 9.6 REFERENCES

Bergman, R. N., Finegood, D. T. and Ader, M. 1985. Assessment of Insulin Sensitivity in Vivo. *Endocr Rev.* 6(1): 45-86

Chase, J. G., Lam, Z. H., Lee, J. Y. and Hwang, K. S. (2002). Active Insulin Infusion Control of the Blood Glucose Derivative. Paper presented at *Proc. of the 7th International Conf on Control, Automation, Robotics and Vision (ICARCV 2002)* in Singapore.

Chase, J. G., Shaw, G. M., Doran, C. V., Hudson, N. H. and Moorhead, K. T. (2003). Derivative Weighted Active Insulin Control Algorithms and Trials. Paper presented at *IFAC Symposium* in Melbourne, Australia.

Doran, C. V., Chase, J. G., Shaw, G. M., Moorhead, K. T. and Hudson, N. H. 2004a. Automated Insulin Infusion Trials in the Icu. *Diabetes Technology and Therapeutics.* 6(2)

Doran, C. V., Moorhead, K. T., Hudson, N. H., Chase, J. G. and Shaw, G. M. 2004b. Derivative Weighted Active Insulin Control Modelling and Clinical Trials for Icu Patients. *Med Eng Phys.* -to appear

Lam, Z. H., Hwang, K. S., Lee, J. Y., Chase, J. G. and Wake, G. C. 2002. Active Insulin Infusion Using Optimal and Derivative-Weighted Control. *Med Eng Phys.* 24(10): 663-672

Patino, J. F., de Pimiento, S. E., Vergara, A., Savino, P., Rodriguez, M. and Escallon, J. 1999. Hypocaloric Support in the Critically Ill. *World J Surg.* 23(6): 553-9

Weissman, C. 1999. Nutrition in the Intensive Care Unit. *Crit Care.* 3(5): R67-75

Woolfson, A. M. 1980. Control of Blood Glucose During Nutritional Support in Ill Patients. *Intensive Care Med.* 7(1): 11-4